A STUDY OF SYNTHETIC METHODOLOGY, STEREOCHEMISTRY, AND CONFORMATIONAL ANALYSIS OF SELECTED 3,7-DIHETERABICYCLO-[3.3.1]NONAN-9-OLS AND DERIVATIVES WITH POTENTIAL MULTI-CLASS ANTIARRHYTHMIC ACTIVITY

By

KEVIN TRAN

Bachelor of Science

University of Central Oklahoma

Edmond, Oklahoma

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A STUDY OF SYNTHETIC METHODOLOGY
STEREOCHEMISTRY, AND CONFORMATION
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WITH POTENTIAL MULTI-CLASS
ANTIARRHYTHMIC
ACTIVITY.

Thesis approved:

K D Berlin
Thesis Advisor

Wolff R

Andrew Mort

Richard A. Bunce

Mark Mitchener

Alfred Larkoski
Dean of Graduate College

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CHAPTER I

HISTORICAL

Sudden Cardiac Death (SCD) is a major health problem in the United States. Each year 400,000-460,000 persons die of unexpected SCD.[72] The term "Sudden Cardiac Death" implies the sudden, abrupt loss of heart function (i.e., cardiac arrest) in a person who may or may not have diagnosed heart disease. It is sudden and unexpected in nature, and a victim can experience shortness of breath, sweating, and fatigue. The failure of the heart muscle to pump blood to the brain results in loss of consciousness within seconds. Gasping for air and seizures follow as death rapidly approaches.[25] SCD is the result of an unresuscitated cardiac arrest, which may be caused by a variety of heart diseases. Most cardiac arrests are due to rapid and/or chaotic activity of the heart (ventricular tachycardia or fibrillation). Some are due to extreme slowing of the heart. These events can be life-threatening or cardiac arrhythmias. Cardiac arrhythmias are a main factor for SCD (Figure 1) and targets for cardiovascular disease research.[35]

The cardiac action potential is a consequence of many transmembrane ionic currents mediated selective, pore-forming protein channels dysfunction. Structural defects of the channels can lead to abnormal electrical activity of the heart which in turn can provoke cardiac arrhythmias.[44] Normal cardiac rhythm results from electrical impulses that start in the sinoatrial (SA) node. They spread throughout the atria to the atrioventricular (AV) node (Figure 2). From there each impulse travels over the many specialized fibers of the His- Purkinje system, distributing the electrical ignition signal to the ventricular muscle

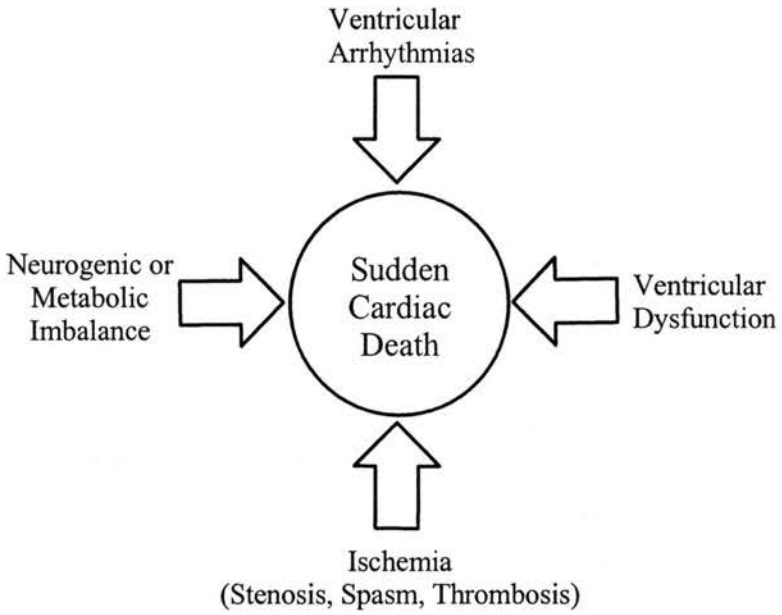


Figure 1. Precipitating factors for sudden cardiac death.

cell. The term arrhythmia refers to an abnormal impulse formation, abnormal impulse propagation, or both.[35] Arrhythmias due to abnormal impulse propagation are explained by the reentry phenomenon, which depends critically upon a relationship between

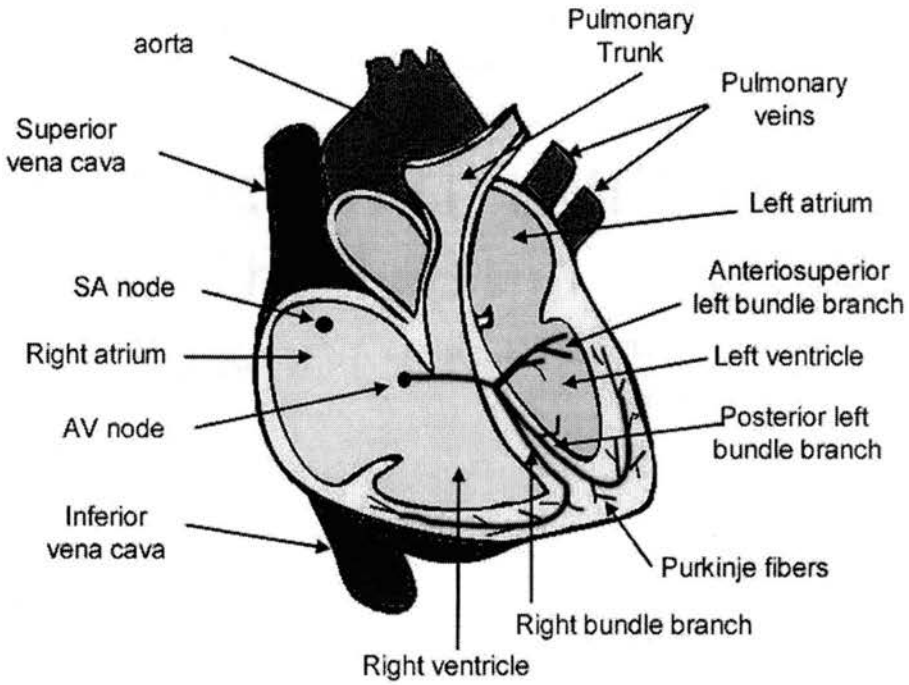


Figure 2. The illustration of SA and AV nodes.

refractoriness and conduction velocity and requires the presence of an unidirectional block in one of the pathways. Factors controlling refractoriness and conduction include action potential duration (APD), sodium and calcium currents, and membrane passive properties.[44]

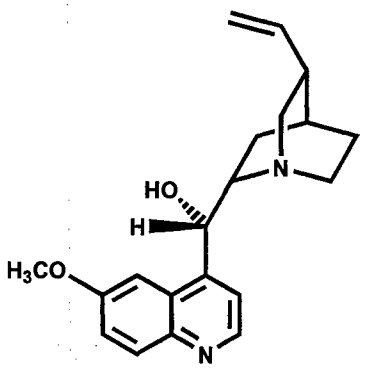
In the last decade, many research groups have successfully synthesized anti-arrhythmic agents (AAA) that are able to modify ionic currents in cardiac tissues by affecting ionic channel pumps, receptors, or second messenger systems.[44] These agents have also been generally classified on the basis of the activities of the agents on the myocardial action potential. These compounds have also been generally classified by the Vaughan Williams Classification system. There are four classes of which Class I is subdivided into three groups according to the effects each agent has on the duration of the action potential (Table I).[71]

Table I. Vaughan Williams Classification.

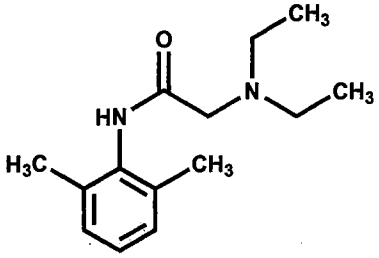
Class	Basic	Active in	Prototypes
I	Sodium channel blockade	Atria, ventricles	
Ia	Increase duration		Quinidine (**1**)
Ib	Decrease duration		Lidocaine (**2**)
Ic	Unchange duration		Flecainide (**3**)[a]
II	Beta (β) blocker	AV node, ventricles	Propranolol (**4**)
III	Potassium fluxes/prolonging the action potential duration	Atria, ventricles	Amiodarone (**5**)
IV	Calcium channel blockade	AV node	Verapamil (**6**), Diltiazem (**7**)

[a] *This prototype is no longer used due to its severe side effects.*

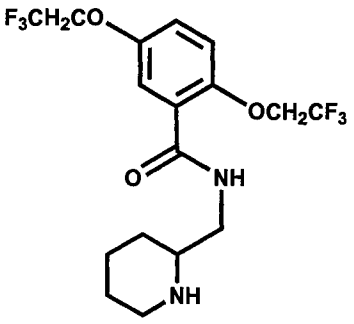
Agents with Class I activity block the fast sodium channels and thereby decrease velocity of the cardiac action potential maximum (the maximum rate of rise of depolarization) V_{max}. Agents with Class II activity are β-blockers, and consequently



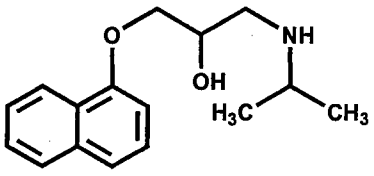
Quinidine
1



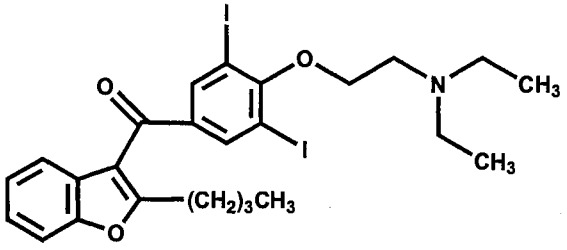
Lidocaine
2



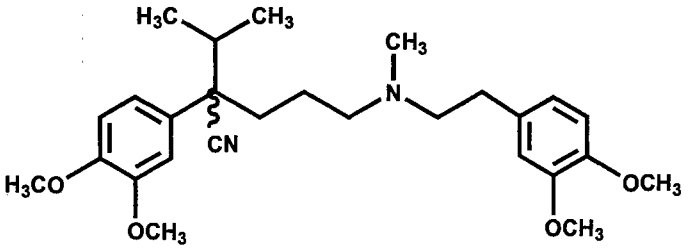
Flecainide
3



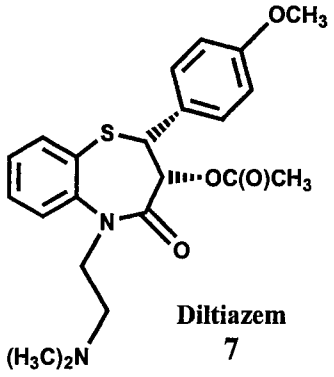
Propranolol
4



Amiodarone
5



Verapamil
6

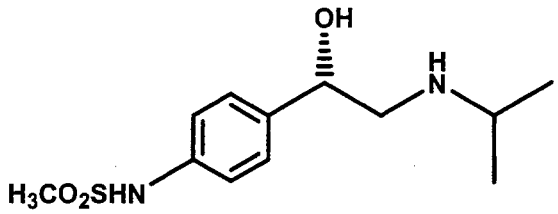


Diltiazem
7

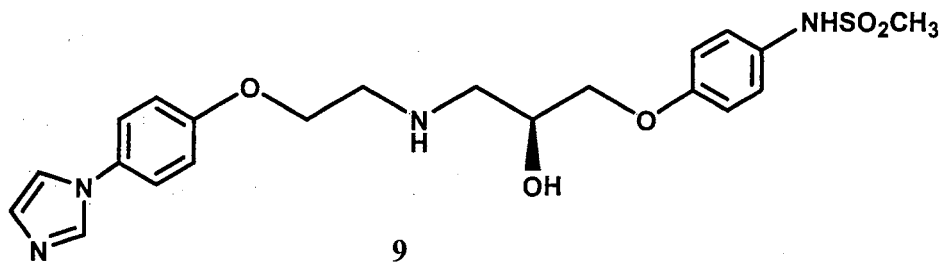
decrease V_{max}. Drugs with Class III activity prolong action potential duration (APD), and the Class IV activity implies calcium channel blockade. However, every agent has its

own limitations, and this is true for those classified by the Vaughan Williams system. Each antiarrhythmic drug in the classification scheme may possess multiple actions.[73] Thus, one drug can belong to more than one Vaughan Williams class. In fact, actions of the AAA in a patient might be better anticipated with a full understanding of the multiple actions of the agents and their metabolites, combined with knowledge of their clinical pharmacology. Consequently, one might predict factors which could influence drug action.[73]

Since the last decade, one of the most recent trends in the synthesis of potent anti-arrhythmic agents is to develop an agent with a specific combination of class actions within a single molecular structure, particularly the combination of class II and III activities. Such an agent would have the potential to act against reentrant arrhythmias at doses below those causing β-blocking hypotension and cardiac depression.[15,20] *d*-Sotalol (**8**) was one of the first published antiarrhythmic agents to possess combined class II and



8 (*d*-Sotalol)

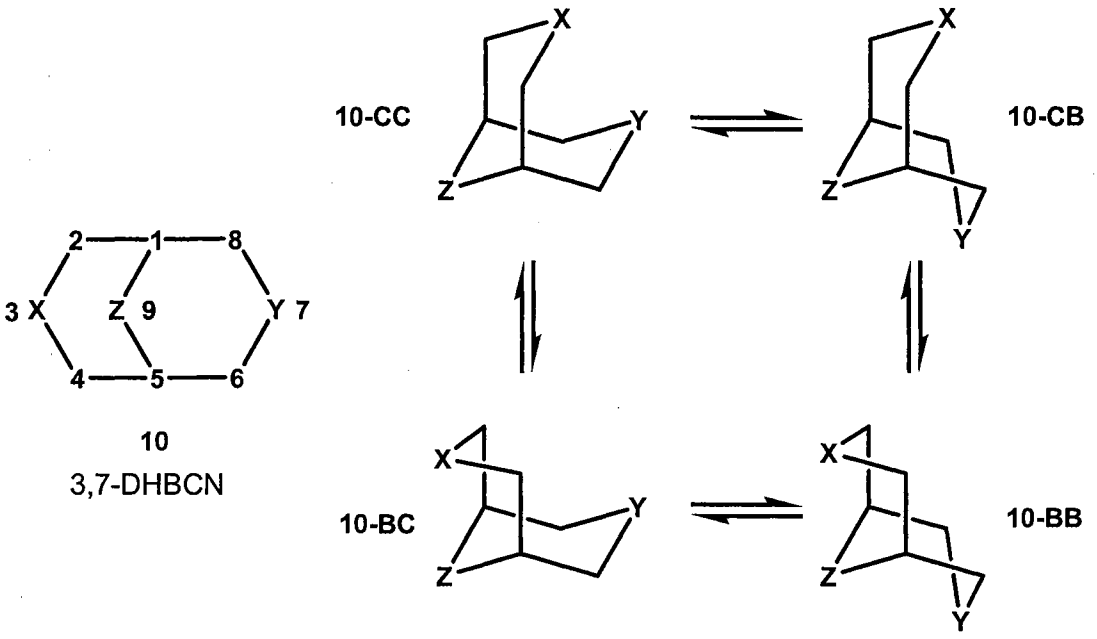


9

III activities.[62] Lis and co-workers have synthesized a series of (aryloxy) propanolamines which have class II and III activities.[39] Moreover, studies in mongrel dog hearts[15]

showed that compound **9** was an even more potent antiarrhythmic agent than *d*-sotalol (**8**) and had even greater selectivity toward class II and III action as well as low toxicity.

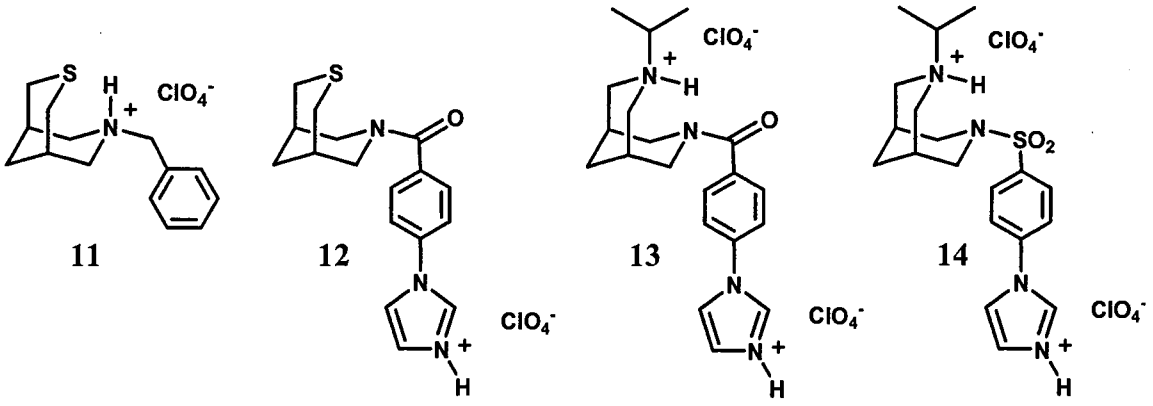
Certain members of the 3,7-diheterabicyclo[3.3.1]nonanes (DHBCN) have been of interest not only for unique conformational and stereochemical considerations but also as potential analgesic and antiarrhythmic agents.[31,74] By obtaining structure-activity relationships, it was found that certain structural modifications in the 3- and 7-positions of DHBCNs **10** could significantly change the observed class Ib and III anti-arrhythmic activity.[5,13,27,55,62] Introduction of some specific functional group at a specific position on a ring can lead to agents with enhanced activity and more than one class action. In addition, it has been clearly reported that DHBCNs possess conformational mobility and as a result can adopt four different conformations,[31,49,74] namely a chair-chair (**10-CC**), boat-chair (**10-BC**), boat-boat (**10-BB**), and chair-boat (**10-CB**). The dynamic properties of these bicyclic systems may result in equilibration between the various four conformers.[5,74]



10
3,7-DHBCN

ANTIARRHYTHMIC PROPERTIES

Our research groups have developed specific synthetic methodology to obtain a series of DHBCNs. These compounds were examined for antiarrhythmic properties in anesthetized dogs in which a mycocardial infarction was induced by ligating the left coronary descending artery. Table II shows the results of a electrophysiological analysis of these agents in comparison to lidocaine (**2**), a class Ib antiarrhythmic agent. The pharmacology of agent **11** has been extensively studied.[18] Salt **11** was found to suppress the heart rate by 29% and to inhibit the induction of reentry of the ventricular tachycardiac, and it was classified as class Ib antiarrhythmic agent.[5] The principal electrophysiologic action of **12** was a prolongation of the action potential duration.[47] This compound suppressed both sustained and nonsustained ventricular tachycardia.



The preliminary results of electrophysiological and antiarrhythmic evaluations indicate that **12** was a class III antiarrhythmic agent.[47] Compound **13** was found to be the best antiarrhythmic agent yet synthesized in our laboratory.[28] The accumulated data on **13** indicated that this agent possessed a combined class Ib/III antiarrhythmic action whereas compound **14** possessed only class III activity.[28]

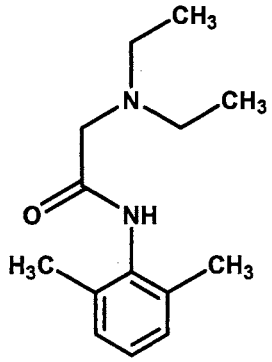
Table II. Antiarrhythmic Properties[a] of Selected 3,7-Diheterabicyclo[3.3.1]nonane Hydroperchlorate.[18,28,47]

Compound	HR[b]	MBP[c]	QT interval[d]	AH interval[e]	HV interval[f]	VERP[g]	NSVT[h]
2	NE[i]	DEC[j]	NE	NE	NE	NE	-
11	NE	INC[k]	NE	NE	INC	INC	+
12	DEC	DEC	INC	INC	INC	INC	+
13	NM[l]	NE	INC	NE	NE	INC	+
14	DEC	DEC	INC	INC	NE	INC	+

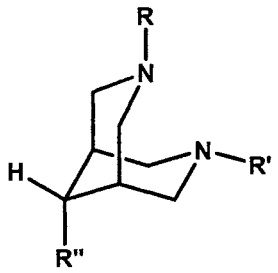
[a] Antiarrhythmic properties are compared to lidocaine (**2**) using doses (3 mg/kg) in which SVT was non-inducible in the DHBCN system while lidocaine (**2**) only reduced the rate of the VT.
[b] HR = Heart Rate (beats/min).
[c] MBP = Mean Blood Pressure (mm Hg).
[d] QT interval = Time (msec) required for the cell to undergo depolarization and repolarization.
[e] AH interval = Time (msec) required for conduction across the cell.
[f] HV interval = A measure of sodium channel action (msec).
[g] VERP = Time (msec) elapsed to complete the QRS complex of the electrocardiogram.
[h] NSVT = Non-Sustained Ventricular Tachycardia.
[i] NE = No Effect.
[j] DEC = Decrease.
[k] INC = Increase.
[l] NM = Not Measured.

As discussed earlier, structural modifications in the 3- and 7-positions of DHBCNs significantly change the observed class Ib and III activities. More recent work focused upon classifying the DHBCNs *via* different class actions based upon modifications in the 9-position of DHBCNs. Several DHBCN derivatives **15** were prepared with an alcohol or an ether functionality in the 9-position and showed enhanced activity (Table III).[45] To assay for antiarrythmic effect, rats were pretreated intravenously with aconitine to induce

Table III. Antiarrhythmic Activity of Bispidine Derivatives 15.[a]



2



15

Agent[b]	R	R'	R"	ED_{50}[c]	LD_{50}[d]	T.I.[e]	R.I.[f]
2				10.0	28.5	3	1
15a	CH_3	CH_3	O_2C-2-naphthyl	0.11	17.0	154	58
15b	CH_3	CH_3	O_2CPh	0.08	9.0	112	39
15c	CH_3	CH_3	OC_6H_4-4-Cl	0.90	52.0	58	21

[a] Reference 45.
[b] Aconotine-induced arrhythmiac in rats.
[c] Effective dose (mg/kg) to restore normal sinus rhythm in 50% of rats tested.
[d] Dose (mg/kg) causing mortality in 50% of tested rats.
[e] Q = Therapeutic Index (T.I.) = LD_{50}/ED_{50}.
[f] Relative Index (R.I.) = T.I. (agent)/T.I. [lidocaine (**2**)].

arrhythmias. Compounds **15a-c** exhibited therapeutic activity several times greater than lidocaine (**2**), which was used as the standard. In addition, compounds **15a-c** increased the refractory period.

Attempted alteration of the 9-position of selected 3,7-DHBCN-9-ONES was also included in the work of Smith.[63] Ketones **16a** and **16b** were subjected to a Mannich condensation with benzylamine, paraformaldehyde, and acetic acid in dry methanol to afford bicyclic ketones **17a** and **17b**. Treatment of ketones **17a** and **17b** with perchloric acid in boiling methanol yielded ketals **18a** and **18b**.[63] A solution of ketone **17b** in benzene or ether was treated with 60% perchloric acid to afford corresponding diol **19**.[63] On the other hand, deoxygenation of ketone **17a** gave, after acidification, **20**. These compounds were examined for multi-class anti-arrhythmic activities in dog models. Anesthetized mongrel dogs were studied 24 h after ligation of the descending coronary artery, and the results are given in Table IV.[63] Ketals **18** and salt **20** exhibited superior antiarrhythmic activity compared to lidocaine (**2**) in terms of not allowing sustained VTs at 3 and 6 mg/kg dosages. Moreover, a small increase in mean blood pressure (MBP) was an added quality. Using **18** and **20**, and with three separate dogs in each case, the VT was abolished completely at the 6 mg/kg level. Lidocaine (**2**) rarely suppressed the induced VT totally, but did reduce the rate of the VT by a maximum of 46%. On the other hand, when the diol was introduced at the C(9) position, as in compound **19**, both a small reduction in the rate of the VT was noted along with a slight drop in MBP at 3 mg/kg. Thus, the small polar groups [H_3CO] at C(9) appeared extremely beneficial for enhancing antiarrhythmic abilities of members 3,7-DHBCN family. In contrast, it was conceivable that the diol **19** was converted *in vivo* to the precursor **17b,** and ketone

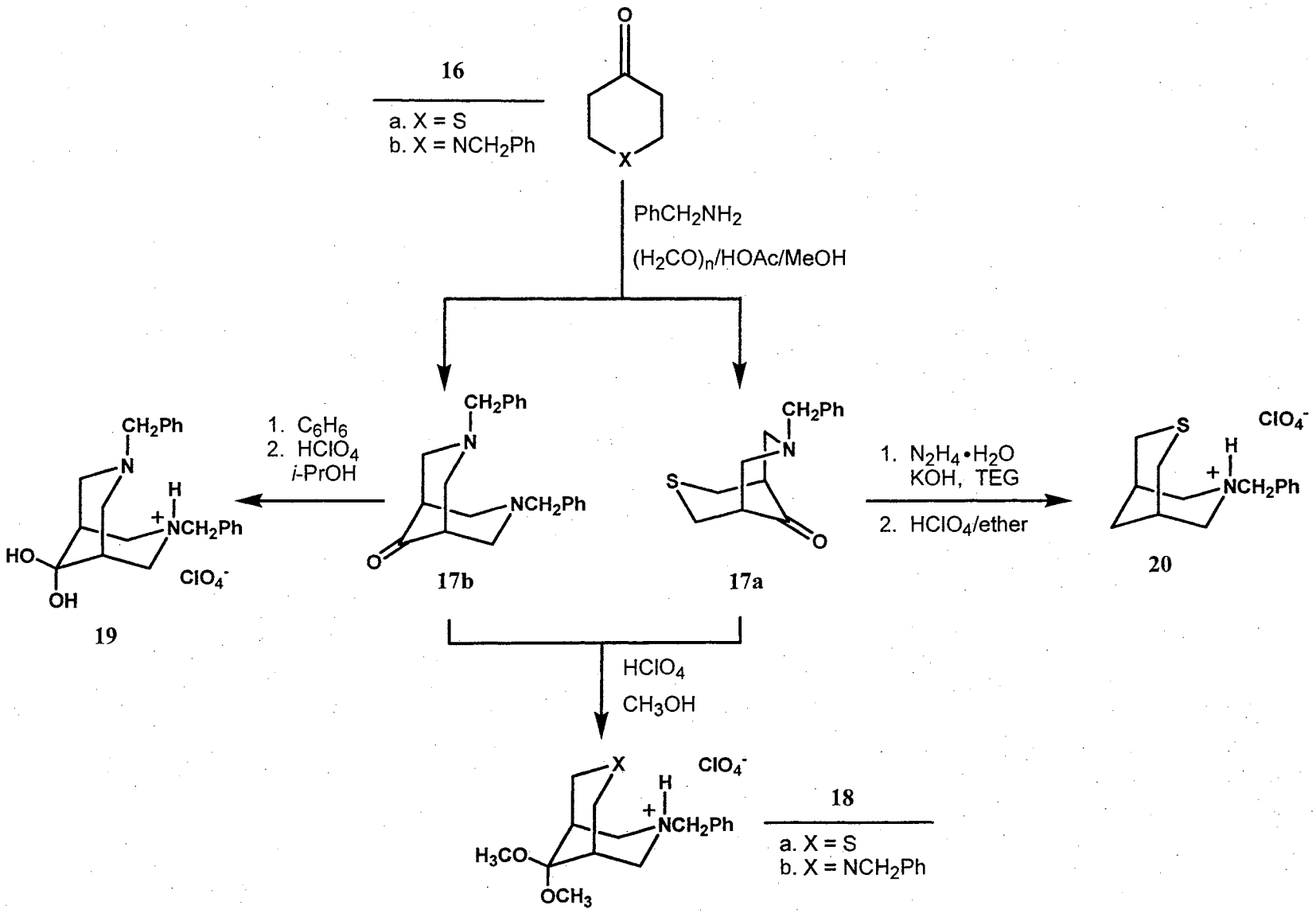
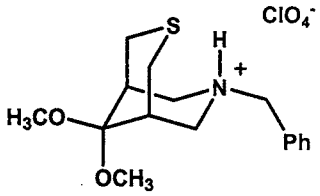
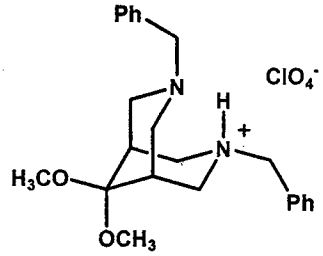
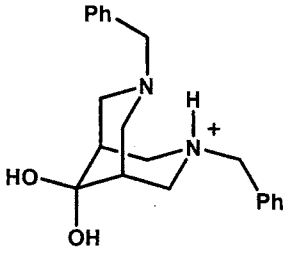
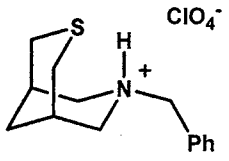

16
a. X = S
b. X = NCH2Ph
PhCH2NH2
(H2CO)n/HOAc/MeOH
1. C6H6
2. HClO4
i-PrOH
1. N2H4•H2O
KOH, TEG
2. HClO4/ether
HClO4
CH3OH
17b
17a
19
20
18
a. X = S
b. X = NCH2Ph

Table IV. Antiarrhythmic Properties of Selected Derivatives of 3,7-DHBCN-9-ones with Modification in the 9-Positions. [a]

Compound		SVT[b]	MBP[c]	SVT	MBP	SVT	MBP
		390	120	NSVT	133	NSVT	130
		390	90	NSVT	99	NSVT	99
	Lidocaine	390		330		330	
18a				300		270	
		330	116	300	120	NSVT	111
		390	90	210	92	NSVT	95
	Lidocaine	360		330		270	
18b		390		300		270	
		390	102	330	95	300	90
	Lidocaine	390		300		210	
19							
		390	90	300	97	270	104
		270	70	NSVT[b]	75	NSVT[b]	82
20	Lidocaine	390		300		270	
		270		270		240	

[a] Reference 63.
[b] SVT/NSVT = Sustain Ventricular Tachycardia/Non Sustain Ventricular Tachycardia.
[c] MBP = Mean Blood Pressure.

members of this family have not shown significant activity in previous examples.[5,18f]

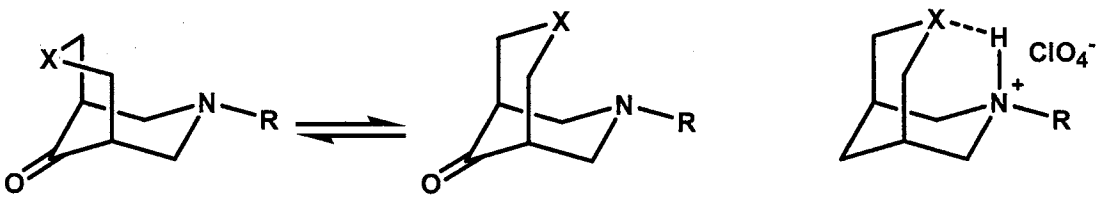
The search for new antiarrhythmic agents remains a viable goal. In continuing efforts to determine structural features which convey optimum antiarrhythmic properties on 3,7-DHBCN and derivatives, we synthesized several substituted systems. Hence, this discussion will mainly focus on the modification of the 9-position of 3,7-diheterabicyclo[3.3.1]nonan-9-ones **21a,b**.

CONFORMATIONAL ASPECTS

Conformational mobility, a unique property which is inherent to the DHBCN ring system, has stimulated a variety of studies concerning the stereochemical and conformational preferences.[1,2,10-12,40,74] Not only are such analyses useful in diagnostic probes for structure elucidation, but such data are also important to understand the observed biological properties and possible the mode of actions of these agents. As stated previously, compounds containing the 3,7-diheterabicyclo[3.3.1]nonane framework can exist in four possible conformations when X and Y are not identical. Although CC and BB conformations are supposedly free from angular strain, nevertheless none are likely entirely free from some destabilizing interactions between non-bonded atoms.[5,74]

Our group has done extensive NMR studies on several members of the 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones[2] which include ketones **21**. An X-ray diffraction analysis of solid ketones **21b** and **21c** showed a preference for a BC conformation which was further supported by variable temperature NMR studies of **21b** in solution.[2,5,18f] A

flattened CC conformation was suggested in solution for **21b**.[2] In previous studies,[2c,23] an enhanced population of the BC conformation in D_3CCN solution at 70 °C was assigned



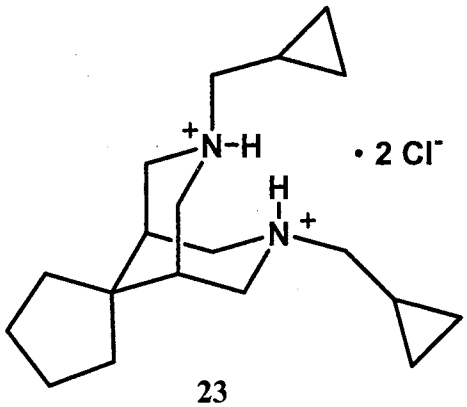
21 **22**

	X	R
a	O	CH_2Ph
b	S	CH_2Ph
c	Se	CH_2Ph
d	NCH_2	CH_2Ph

	X	R
a	S	CH_2Ph
b	Se	CH_2Ph

to ketone **21b** by ^{17}O NMR spectroscopy. In this case, the ring bearing the benzyl group existed in a chair form and thus appeared somewhat biased. This assignment was derived on the basis of the observation that an upfield shift of 5-7 ppm [due to increase shielding at C(9)] was observed for ^{17}O for C=O in each system.[2c] This observation appeared defensible only if a significant interaction existed between the lone pair in the heteroatom and the pi orbital of the carbonyl group. Thus, it was tentatively concluded that a BC conformer could give rise to such an effect. Ketones **21a,b** were also subjects for conformational analyses in the gas phase. [2e] The ab initio methods with Gaussian 94[5] calculations suggested that in solution the CC forms of ketones **21a,b** were favored over CB forms by approximately 0.544 and 0.892 kcal/mol.[2e] ^1H NMR analysis of **21a** showed chemical shifts in the bicyclic system to be in the following order: $\delta_{H(1,5)} < \delta_{H(6,8)}$

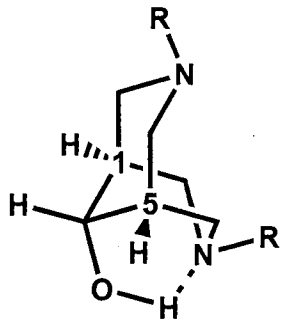
$< \delta_{H(CH2Ph)} < \delta_{H(2,4)} < \delta_{H(aromatic)}$, and that of **21b** in the following order: $\delta_{H(1,5)} < \delta_{H(6,8)} < \delta_{H(2,4)} < \delta_{H(CH2Ph)} < \delta_{H(aromatic)}$.[2a,5] The chemical shifts were assigned partially on the basis of electronegativity effects of the heteroatoms on the chemical shift of the α-protons and upon extensive proton-decoupling studies. However, when ketones **21b,c** were reduced to the corresponding hydrocarbons, followed by salt formation, a CC conformation resulted for **22a,b**.[2] Both systems possess rings with ends containing N and S (or selenium) which were flattened as indicated by the torsion angular measurement.[2]



23

Based upon ^{1}H and ^{13}C NMR spectroscopic data,[26] Finner and co-workers found that two piperidine rings of the diprotonated tedisamil dihydrochloride (**23**), a class II antiarrhythmic agent, were flattened CC conformations in solutions as well as in the solid state.[26] These two CC conformations were stabilized by strong hydrogen bonds, in the solid state to the chlorine anion and in aqueous solution to a water molecule. An examination of the trajectories of the two Molecular Dynamics runs (CC and CB) yielded a much more stable, hydrogen-bonded water cluster for the CC conformation in **23**.[26] The fluctuations for the BC system were much higher; no definite $H_2O....^{+}H$-N contact

remained stable within a 3 Å sphere for more than 3 picoseconds. The results obtained from AM1 calculations also indicated that a significant change in the preferred conformation of **23** towards a CC form occurs if the medium is changed from "quasi gas phase" to a polar environment, presumably forced by the formation of strong hydrogen bonds. Moreover, an additional flattening of the two piperidine rings compensated for the Coulomb repulsion between the two charged nitrogens and favored the CC conformations.[26]



24

a. R = $CH_2CH_2OCH_2Me$
b. R = $CH_2CH_2CH_2OCHMe_2$

Conformational studies of a few 3,7-DHBCN members was recently conducted by Berlin, Yu, and co-workers.[11] The spatial structures of 3,7-dialkylated-3,7-diazabicyclo-[3.3.1]nonan-9-ols were investigated with the aid of ^1H and ^{13}C NMR spectroscopy. Based upon the obtained vicinal coupling constants of certain protons,[11] it was established that the bicyclic systems **24** possessed chair-boat (CB) conformations. The ^1H NMR spectrum of alcohol **24** showed one triplet with splitting exceeding 10 Hz. The triplet formed arose when two couplings overlapped. It is known that for rigid chair-form piperidine systems the coupling constants are fairly characteristic, and values greater than

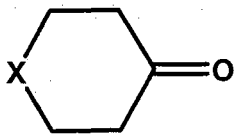
10 Hz may correspond to the interaction of both geminal and vicinal protons disposed diaxially relative to the plane of the ring.[16] It was considered that the 1-H and 5-H protons in compound **24** are equatorial as a result of the prescribed method of linking the rings. If it was assumed that both rings were in chair forms, then the appearance of a large vicinal constant was impossible since there are no trans-diaxially disposed protons. For 3,7-diazabicyclo[3.3.1]nonanes having a CC conformation the vicinal constants lie in a range 1 to 7 Hz.[11] This means that only 1 variant of the explanation remained acceptable, which was that one of the rings in **24** assumed a boat form. In addition, an X-ray analysis also suggested that a stabilization factor for the CB conformation in **24** was the intramolecular hydrogen bond between the unshared pair of electron on the nitrogen atom and the hydrogen atom of the hydroxyl groups.[11]

CHAPTER II

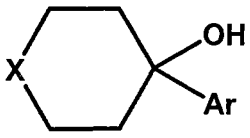
RESULTS and DISCUSSIONS

Certain members of the 3,7-diheterabicyclo[3.3.1]nonane family display anti-arrhythmic action in the 1-4 day infarcted dog heart with the use of lidocaine (**2**) as the clinical standard.[12] The potential utility of these agents is to help prevent lethal arrhythmias, which could lead to sudden cardiac death. Slight structural modifications in the 9-position of DHBCN can significantly alter the antiarrhythmic action as previously discussed in Chapter I.[40,45,63] Therefore, further characterization of structure-activity relationships could allow the incorporation of structural features which might enhance multi-class antiarrhythmic activity in this heterocyclic family.

Starting from ketones **25**, a first emphasis for this research was to develop a series of monocyclic tertiary alcohols **26**. These alcohols were prepared from ketones **25** and served as model systems for comparison with bicyclic alcohols to be prepared. Interestingly, ketone **25** has found use as a synthon in the generation of part of the vitamin D_3 ring A.[34] The simple alcohols could also possess analgesic and muscle relaxing activities. Recent preparations of 4-*t*-butylthiopyran-4-ol and 4-vinylthiopyran-4-ol revealed that these agents possess analgesic and muscle relaxing activities in mice.[64]



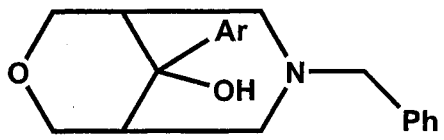
25



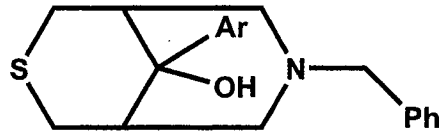
26

X = 0, S

This research has developed a synthetic methodology to obtain several new and novel 3-hetera-7-azabicyclo[3.3.1]nonan-9-ols. In addition to new alcohols **26**, a series of bicyclic alcohols **27** and **28** from title ketones **21a** and **21b**, with potential multi-class antiarrhythmic activity, were prepared.



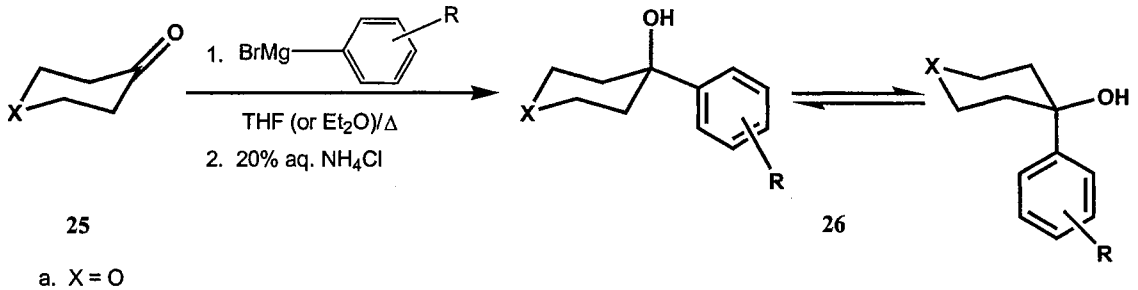
27



28

SYNTHETIC METHODOLOGY

Tetrahydro-4*H*-pyran-4-one (**25a**) and tetrahydrothiopyran-4-one (**25b**) served as starting materials to obtain heterocycles **26.** The condensations of ketones **25** with selected aryl Grignard reagents in the ratio 1:2 proceeded well under mild conditions in anhydrous ether or THF to give expected crystalline, monocyclic tertiary alcohols **26.**



25

a. X = O

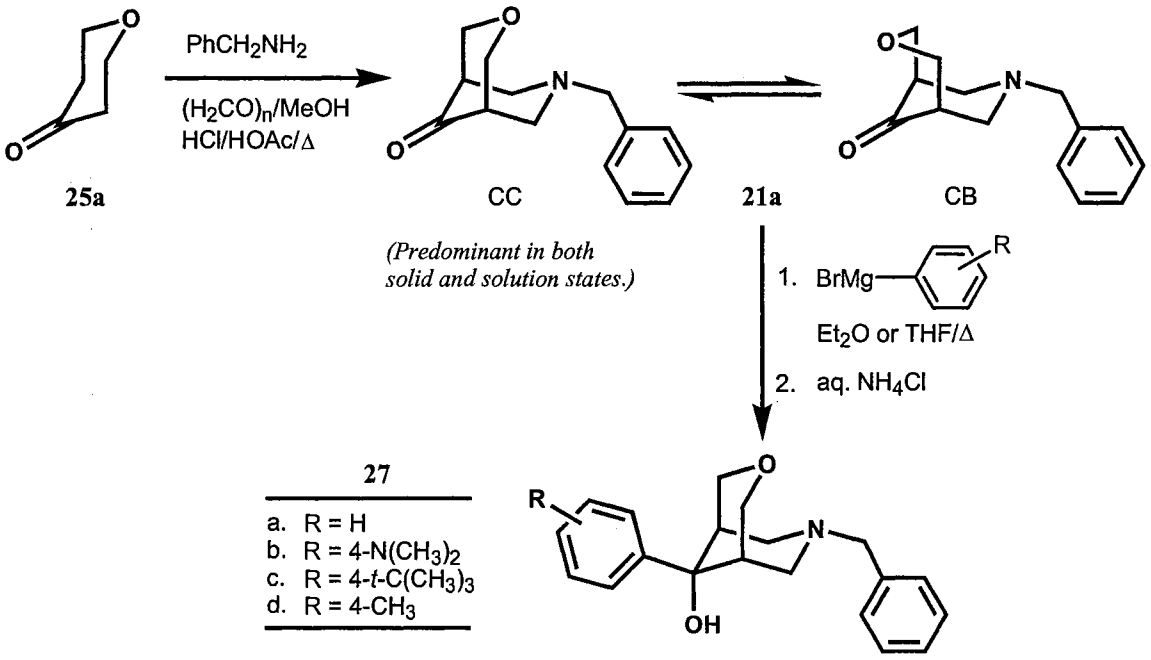
b. X = S

26

a. X = O, R = H (88%)	g. X = S, R = H (72%)
b. X = O, R = 4-Cl (94%)	h. X = S, R = 4-Cl(91%)
c. X = O, R = 4-$N(CH_3)_2$ (77%)	i. X = S, R = 4-$N(CH_3)_2$ (70%)
d. X = O, R = 3,5-$(CH_3)_2$ (74%)	j. X = S, R = 3,5-$(CH_3)_2$ (75%)
e. X = O, R = 4-CH_3 (74%)	k. X = S, R = 4-CH_3 (69%)
f. X = O, R = 4-$C(CH_3)_3$ (67%)	l. X = S, R = 4-$C(CH_3)_3$ (68%)

Yields were good to excellent and ranged from 68% to 94% with a minimal workup. Comparisons of ^{1}H and ^{13}C NMR chemical shifts and conformations among the model systems **26** and bicyclic alcohols **27, 28** will be discussed later in this dissertation. The 1,2-additions of aryl Grignard reagents to the carbonyl groups in the ketones **25** resulted in the formation of tertiary alcohols existing in chair forms with aryl groups in pseudo-equatorial positions.

Similarly, pyranone **25a** and thiopyranone **25b** also serve as precursors in the synthesis of target bicyclic alcohols containing heteroatoms S and/or O. A double Mannich condensation[68] of ketones **25** was utilized in the synthesis of 3-hetera-7-azabicyclo[3.3.1]nonan-9-ones **21**. Condensation of **25a** with paraformaldehyde, benzyl

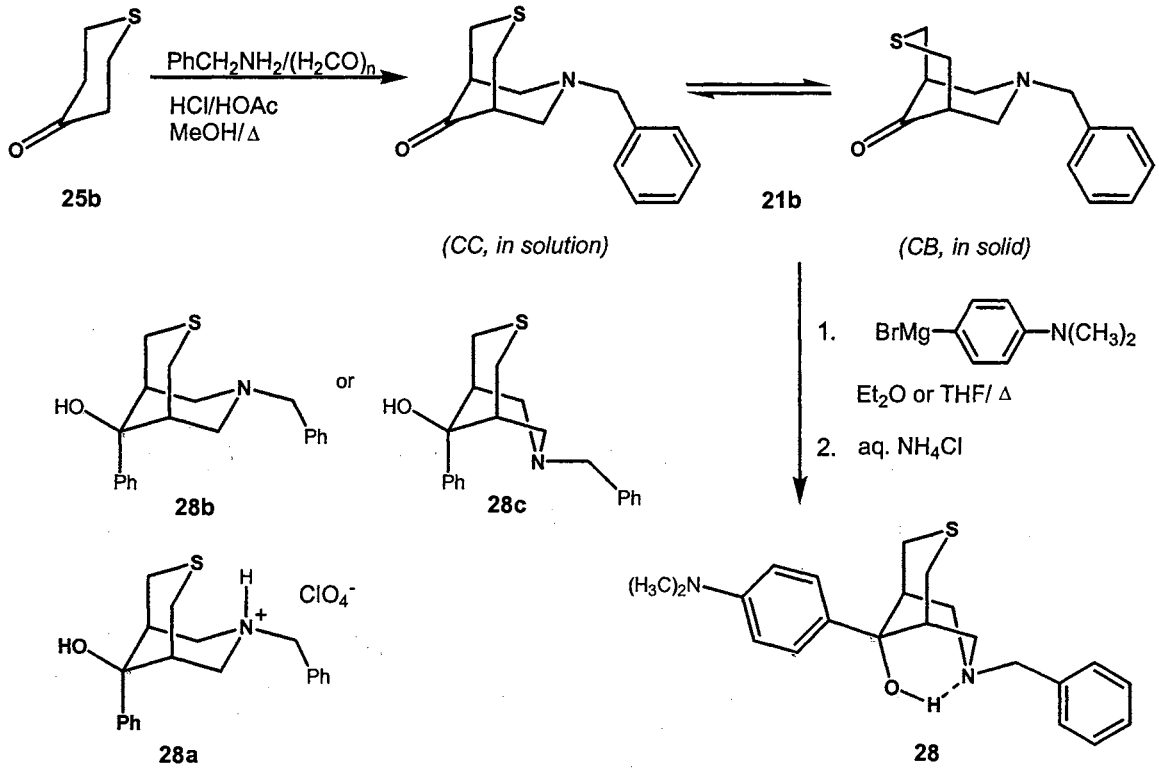


amine, glacial acetic acid and one-half equivalent (with respect to the amine) of HCl (37%) gave (after workup) ketone **21a**. It had been previously discovered that the addition of HCl could increase the yield of ketones prepared by the Mannich

condensation from 25 % to 56%.[21] It is speculated that the reaction pH plays a critical role in the condensation kinetics, perhaps in accelerating the formation of the intermediate iminium ion. The previous work[21] also reported that the addition of a second equal portion of paraformaldehyde, after 10 h of reflux, increased the isolated yields of a Mannich product from 56-57% to 69-76%. This phenomenon has not been completely understood, but one possible explanation might be that paraformaldehyde formed side products. A conformational study of **21a** in the gas phase[2e] by ab initio methods with Gaussian 94 calculations[29] suggested that the CC form of **21a** was favored over the BC form by about 0.544 kcal/mol. The bicyclic system actually crystallized in the CC form.[2e] The 1,2-addition of selected Grignard reagents to the ketone **21a** in dry anhydrous ether or THF with refluxing produced bicyclic alcohols **27** in modest yields of 42-45%. Such yields are likely to be encountered in the synthesis of tertiary alcohols with bulky alkyl groups in which side reactions compete more effectively.[61] The two most important side reactions are enolization and reduction.[61] Enolization (not possible in **21a**) may occur if the ketone has at least one hydrogen on either of the α-carbons and reduction may occur when the Grignard reagent has a hydrogen on its β-carbon.[61]

A double Mannich condensation was also utilized in synthesizing ketone **21b** from ketone **25b**[5] using the same conditions as for ketone **21a**. Treatment of the thiopyranone **25b** with benzylamine and paraformaldehyde in the presence of HCl and glacial acetic acid in methanol gave **21b.**[5] A previous study[2e] reported that the CC conformer of **21b** was favored over the BC conformer by about 0.892 kcal/mol by ab initio methods with Gaussian 94 calculations. However, the bicyclic system **21b** crystallized in the BC

form.[5] Boiling ketone **21b** with selected Grignard reagents in dry THF gave tertiary alcohols **28**, respectively. Interestingly and unexpectedly, the addition of a big bulky



aryl group to the C(9) position of title ketone **21b** dramatically changed the conformation of the bicyclic system. Alcohol **28** crystallized in a CB form, *not a CC or BC form,* with the aryl group on the same side of the ring as the heteroatom S and in a pseudo equatorial position with respect to nitrogen ring. This was very surprising since **28a** has been reported as a CC system when isolated as a hydroperchlorate.[5] Moreover, this salt **28a** has the phenyl ring 'anti' to the sulfur atom[5] rather than 'syn' to the sulfur atom as in **28**. There is no obvious reason for the differences observed except for the possibility that the composition and structure of the Grignard reagent from *p*-$(CH_3)_2N$-C_6H_4-Br differed significantly in THF leading to **28** and from PhMgBr/ether leading to the CC form in **28a**.[5] Of course, **28b** could exist as a CB form **28c** in the solid state, but the later has not been isolated.

CONFORMATIONAL ANALYSIS

NMR spectroscopy and X-ray crystal analyses are crucial tools needed to identify the conformational preferences of 3,7-diheterabicyclo[3.3.1]nonanes in solution and in the solid state, respectively. Analyses of this type can be useful in understanding biological properties and possibly an agent's mode of action. While X-ray crystal analysis gives a positive structure in the solid state, extrapolation to the major conformers present in solution must be exercised with caution. One study seemed to indicate that a BC $\rightleftharpoons$ CB equilibrium[66] may operate in many DHBCN's in solution, but other work has indicated that these systems often assume one heavily preferred conformation.[1] Definite proof for a particular conformation of a DHBCN in solution remains difficult. Some of the factors that probably lead to a preferred conformation of these systems are (i) steric repulsion of the heteroatoms, (ii) dipole repulsion, (iii) lone pair orbital repulsion, and/or (iv) intramolecular hydrogen bonding involving a proton on one heteroatom at the 3-position, for example, with the heteroatom at the 7-position.

Chemical shifts in the ^{1}H and ^{13}C NMR spectra of compounds **26a-l** were assigned partially on the basis of electronegativity effects of the heteroatoms on the protons and carbons at the α positions. If a flattened chair is assumed for the heterocyclic ring, the aryl group would be expected to occupy a pseudo-equatorial position. The γ-shielding effects of groups larger than hydrogen, such as the axial O-H group in **26**, are known[51] in simple cyclohexane rings. Such steric effects can induce conformational changes in similar systems as reflected in NMR analysis.[22] The configurations of the 4-pyranols was corroborated by the ^{13}C chemical shifts data (Table V). It was noted that shielding at C(4) depended largely upon the configuration of the hydroxyl group. An axial hydroxyl

Table V. ^{13}C Chemical Shifts of Alcohols 26a-l (ppm, $DCCl_3$).

ppm	26a	26b	26c	26d	26e	26f	26g	26h	26i	26j	26k	26l
$C^{\alpha}_{(3,5)}$	38.58	38.47	38.65	38.67	38.74	38.72	39.43	39.33	39.61	39.55	39.55	39.59
$C^{\beta}_{(2,6)}$	63.74	63.57	63.93	63.80	63.87	63.91	24.08	23.96	24.34	24.17	24.19	24.26
C^{γ}_{4}	70.38	70.05	69.81	70.31	70.38	70.44	71.80	71.61	71.19	71.75	71.64	71.64
CH_3	*X*	*X*	38.65	21.41	20.91	31.28	*X*	*X*	40.52	21.44	20.88	31.31
C	*X*	*X*	*X*	*X*	*X*	34.41	*X*	*X*	*X*	*X*	*X*	34.42
$C_{1'}$	148.04	146.64	148.01	148.11	136.87	144.98	148.93	147.45	125.05	149.05	146.13	146.02
$C_{2',6'}$	127.10	128.40	125.21	122.18	124.32	125.37	127.02	128.40	125.98	121.98	124.11	125.35
$C_{3',5'}$	124.38	125.94	112.30	137.83	129.10	124.11	128.36	125.74	112.31	137.90	129.05	123.98
$C_{4'}$	128.36	132.78	149.63	128.69	145.12	150.18	124.15	132.77	149.54	128.64	136.70	150.03

X = not applicable, carbons on aromatic ring are indicated as numbers with apostrophes.

group commonly shields the hydroxyl-bearing carbon by about 5 ppm as found for epimeric alicyclic alcohols.[51] Note ^{13}C shifts for C4 have a narrow range, implying a common orientation.

Alcohol **26j** was selected for an in depth NMR analysis. The 2D gHMQC NMR spectrum was obtained on **26j** to determine the connectivities of protons and carbons, thereby making peak assignments for ^{1}H and ^{13}C more certain. The gHMQC spectrum **26j** (Figure 3) serves as an example for the other systems. The ^{13}C NMR spectrum of **26j** was plotted along the horizontal axis of the gHMQC spectrum while the proton spectrum of the same molecule was plotted along the vertical axis. A vertical line taken from a peak on the gHMQC spectrum established which peak on the carbon spectrum correlated with a given peak in the gHMQC spectrum while a horizontal line established the correlation to a peak in the proton spectrum. Thus, in the gHMQC spectrum of **26j**, the peak labeled **A** (Figure 3) shows a correlation between $C_{(3,5)}$ and $H_{(3,5)a}$, while **B** indicates a correlation of $C_{(3,5)}$ and $H_{(3,5)e}$. Signal **C** belongs to the CH_3 groups. Signal **D** represents a correlation between $C_{(2,6)}$ and $H_{(2,6)a}$, while **E** exhibits a correlation between $C_{(2,6)}$ and $H_{(2,6)e}$. Both **F** and **G** are for aryl carbons and hydrogens.

Although the ^{1}H and ^{13}C analyses suggested a single conformer for each alcohol with some long range couplings being visible in individual patterns, a variable low-temperature ^{1}H NMR analysis of **26j** was performed. The ^{1}H spectra of **26j** in CD_2Cl_2 were obtained at 28 °C, 0 °C, -60 °C, -78 °C, and -88 °C using the 400 MHz NMR unit operating at 399.899 MHz. Unfortunately, all of the spectra (Figure 4) showed similar shifts and patterns at all temperatures with the exceptions that at low temperatures -60 °C to -88 °C the signal for the hydroxyl proton was shifted from δ 1.45 to δ 2.62 (-78 °C)

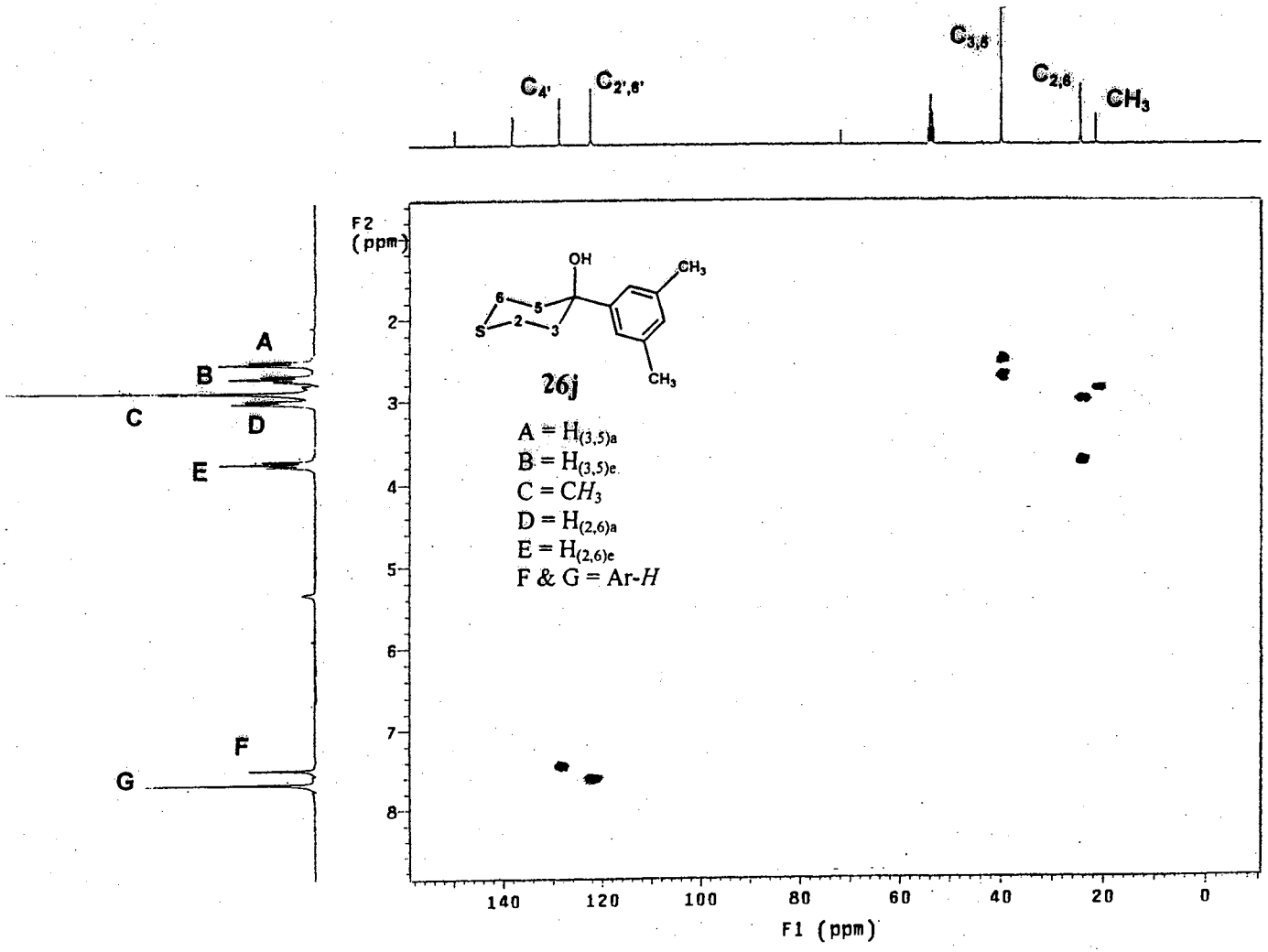


Figure 3. 2D gHMQC Spectrum of **26j**.

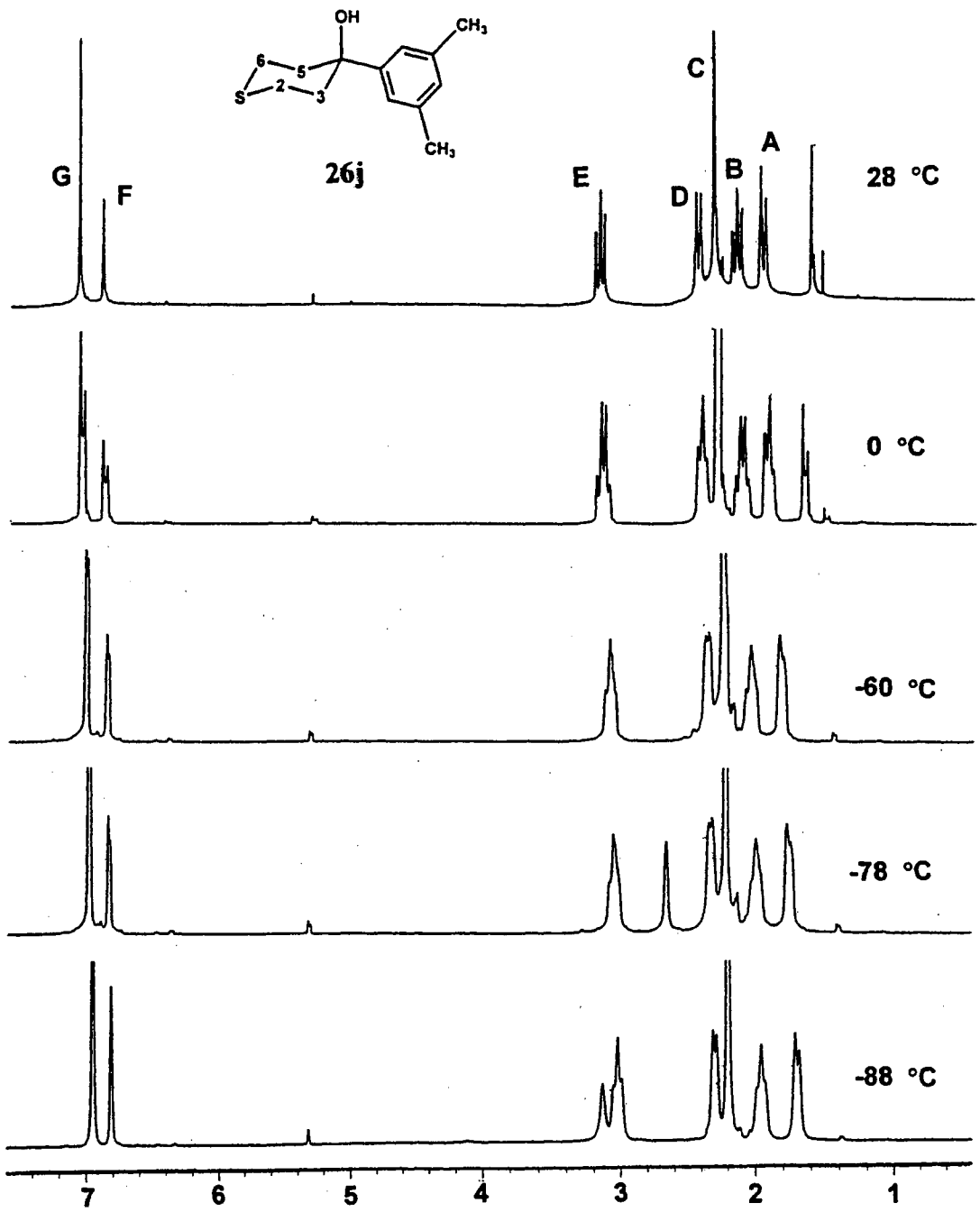


Figure 4. Variable-Temperature ^{1}H NMR Spectra of **26j**.

and to δ 3.12 (-88 °C), respectively. The integration of a full spectrum of **26j** in CD_2Cl_2 at -60 °C showed the region of δ 1.90-2.38 had one proton more than any other pattern in the same region. Thus, it suggested that at -60 °C, a signal for hydroxyl proton was buried somewhere in a region of δ 1.90-2.38. It is well known that the chemical shift of the OH proton is concentration dependent.[50] The possibility exists for the dimerization or trimerization of two or three alcohol molecules in the solution at low temperature -60 °C to -88 °C. It was recently reported[53] that at low temperatures two or three molecules with NH and/or OH groups may form a low-barrier hydrogen bond (Figure 5) which likely

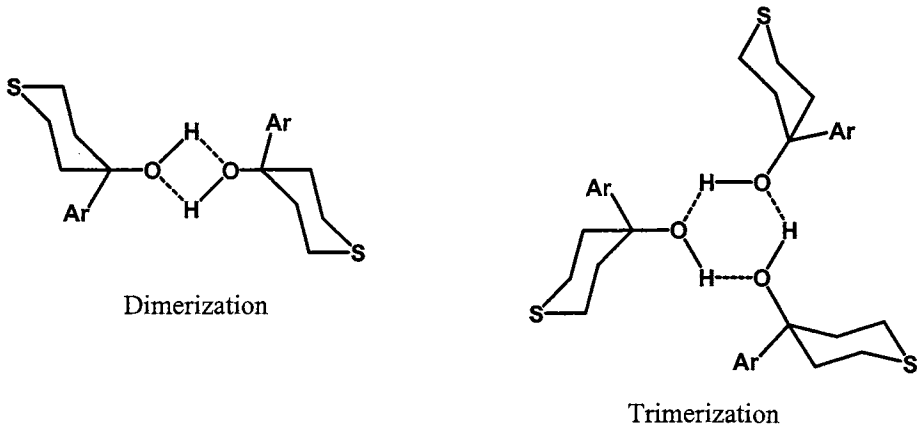


Figure 5. The possible dimer and trimer of **26j**.

affects the chemical shift of the proton on the OH group. At this time there does not appear to be another obvious argument that is tenable to explain our result with **26j**. In addition, to assure that a singlet at δ 1.45 belonged to OH group, the D_2O-exchange experiment was conducted. Expectedly, the obtained spectrum (Figure 6) showed the disappearance of a singlet peak at δ 1.45 and the appearance of another singlet peak at δ 4.82. This proved the singlet at δ 1.45 ppm belonged to the OH group of **26j**, and the singlet signal at δ 4.82 is the HOD peak from D_2O exchange. Despite the ^1H NMR

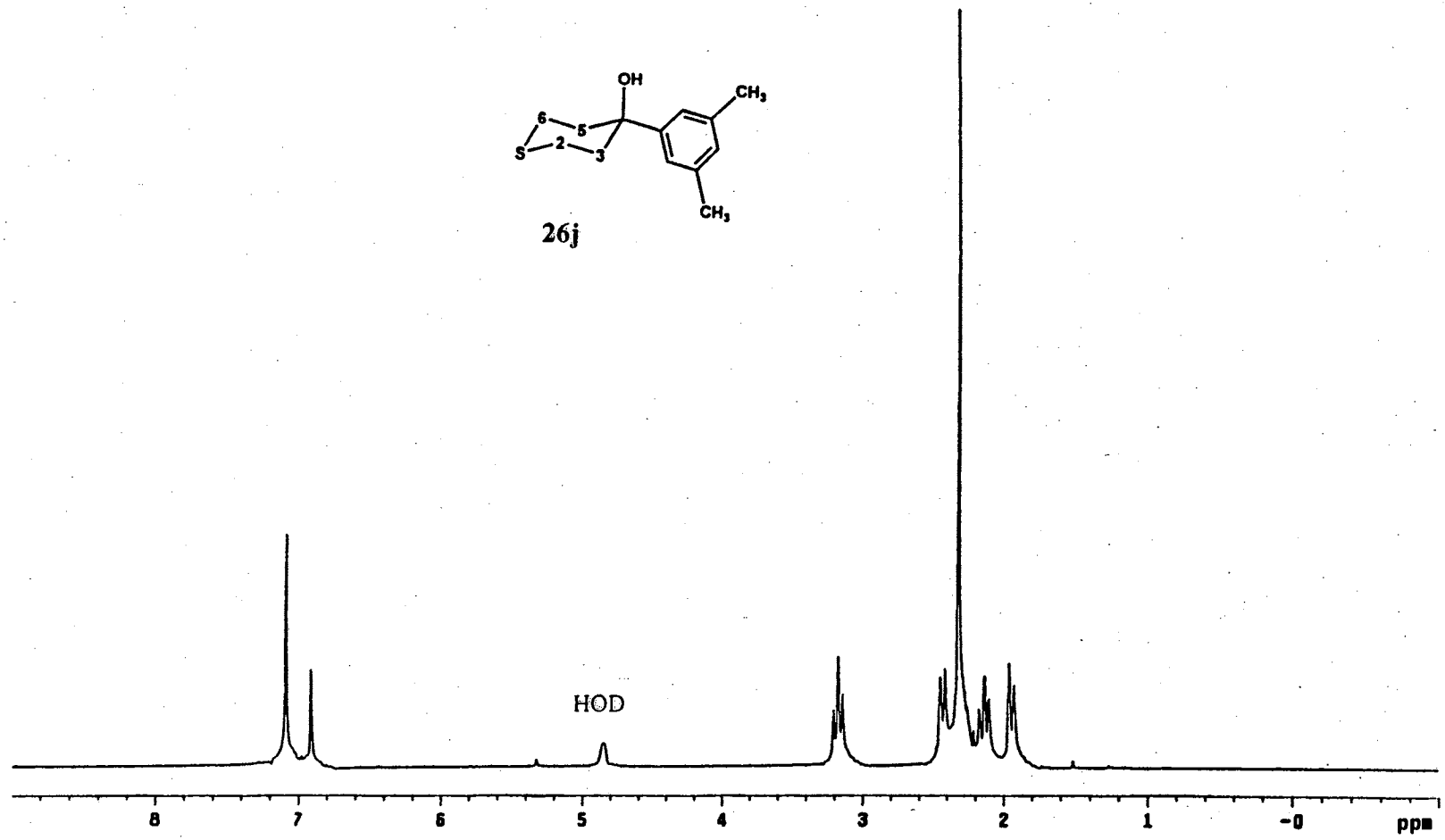
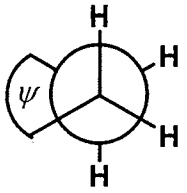


Figure 6. D_2O-Exchange ^1H NMR Spectrum of **26j**.

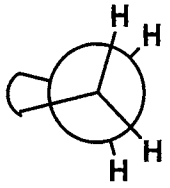
analyses suggesting a single conformer, it is not possible to completely eliminate a small, but dynamic equilibrium involving more than one conformer of **26j** at room temperature. Either ring reversal is not yet frozen out and/or the energy barrier between two individual conformers is below -88 °C. It is tentatively assumed that the major conformer is that with the aryl group in a pseudo equatorial position in D_2CCl_2 or $DCCl_3$ for **26j** at room temperature.

The shape of a ring system can also be estimated *via* analysis of vicinal NMR coupling constants.[36,37] A mobile ring system such as **26j** permits the measurement of two average coupling constants in a CH_2-CH_2 fragment, $J_{trans} = 0.5(J_{aa} + J_{ee})$ and $J_{cis} = 0.5(J_{ae} + J_{ea})$. The ratio, $R = J_{trans} / J_{cis}$, was found to be free of all dependence on the electronegativity and orientation of substituents attached to the CH_2-CH_2 fragment and



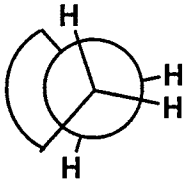
31

$(R = 1.9\text{-}2.2,\ \psi = 56\text{-}58°)$



31a

$(R < 1.8,\ \psi < 55°)$



31b

$(R > 2.3,\ \psi > 59°)$

dependent only upon the conformation.[36] The R-value method[37] was utilized to assess the nature of the distortion present in the ring. In a distortion-free CH_2-CH_2 fragment (**31**) of a six-membered ring, the ratio R of the average vicinal J_{trans} to the average vicinal J_{cis} is normally in a range 1.9-2.2.[37] A flattening of this fragment is related (eclipsings of the substituents, **31a**) to a lower R value. A puckering (**31b**) raises R. The R value is directly related to the internal dihedral angle ψ by equation 1. Thus, the undistorted R

$$\cos \psi = [3/(2 + 4R)]^{1/2} \qquad \text{(eq. 1)}$$

value of 1.9-2.2 corresponds to a torsional angle ψ of 56-58°, in agreement with the non-tetrahedral geometry of cyclohexane. The flattened geometry (R<1.8) corresponds to a ψ < 55°, and the puckered geometry (R > 2.3) corresponds to a ψ > 59°.

The calculation of the distortion angles of system **26j** using equation 1 suggested that the thia ring is flattened, R (= 1.07) < 1.8 and ψ (= 46.3°) < 55°.

$$J_{trans} = J_{1,3} = J_{2,4} = 14.1 \text{ Hz}$$

$$J_{cis} = J_{1,4} = J_{2,3} = 13.2 \text{ Hz}$$

$$R = \frac{J_{trans}}{J_{cis}} = \frac{14.1Hz}{13.2Hz} = 1.07$$

(eq. 1) $$\cos\Psi = \left(\frac{3}{2+4R}\right)^{1/2} = \left(\frac{3}{2+4(1.07)}\right)^{1/2} = 0.69$$

Thereby, $$\psi = \cos^{-1} 0.69 = 46.3°$$

To establish the structure, an X-ray diffraction analysis was also performed on a single crystal of **26j**. The X-ray data demonstrated that the aryl group was clearly attached to C(4) at a pseudo-equatorial position (Figure 7). The X-ray diagram also

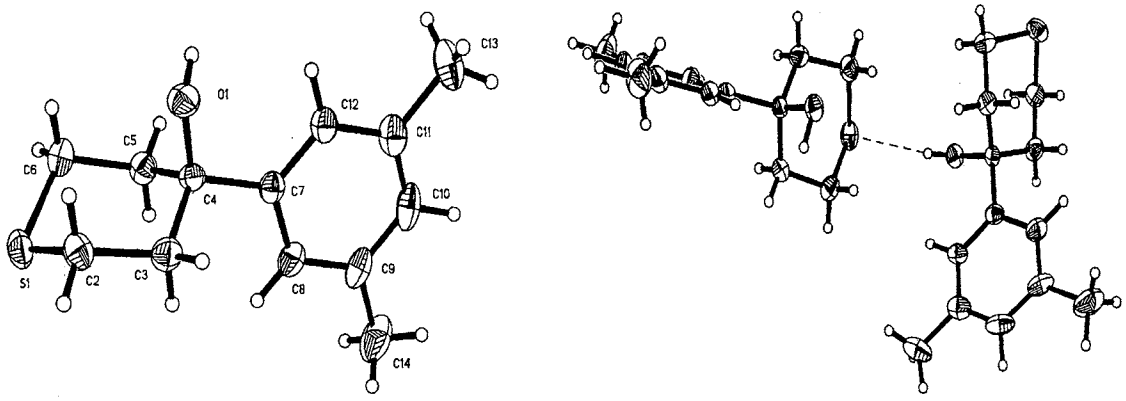


Figure 7. Perspective view of **26j**.

showed that there were two crystal molecules within an unit cell (Figure 7), connected to each other through a weak intermolecular hydrogen bond between a hydrogen atom of the hydroxyl group on one molecule and the unshared pair electrons on the sulfur atom of another molecule. The torsion angles, crystal data, bond lengths and bond angles of the heterocyclic **26j** are given in Tables VI, VII, and VIII. The sum of the theoretical torsion

Table VI. Torsion Angles of 26j.

S1-C2-C3-C4	-61.3°
C2-C3-C4-C5	-56.4°
C3-C4-C5-C6	56.6°
C4-C5-C6-S1	-61.4°
C5-C6-S1-C2	57.3°
C6-S1-C2-C3	-57.1°
Total:	350.1°
Theoretical:	360.0°

angles for an alicyclic 6-member ring would be 360.0° if the ring were totally flat. The total observed torsion angles in **26j** is 350.1°, indicating a flattening near the sulfur end of the molecule. From another point of view, the plane of the base of the chair (C2-C3-C5-C6) subtends an angle of 51.8° with the S1-C2-C6 plane and an angle of 49.6° with the C3-C4-C6 plane. The interplanar angles would each be 60° if the chair had theoretical geometry. The angles are smaller, and thus the ends of the chair are each flattened by about 10° from ideal.

Table VII. Crystal Data and Structure Refinement for 26j.

Mol. Formula	$C_{13}H_{18}OS$
MWT	222.33
Temperature	293 (2) K
Wavelength	0.71073 A
Crystal System	Orthorhombic
Space group	Pna2(1)
Cell Dimentions	a = 9.729 (10) Å $\alpha = 90°$
	b =12.846 (2) Å $\beta = 90°$
	c = 9.970 (10) Å $\gamma = 90°$
Volume	1246 (3) $Å^3$
Z, Calculated density	4, 1.185 mg/m^3
Absorption coefficient	0.233 mm^{-1}
F (000)	480
Crystal size	0.15 x 0.15 x 0.2 mm
Theta range for data collection	2.59° to 27.10°
Index ranges	$-1 \leq h \leq 12, -16 \leq k \leq 1, -12 \leq l \leq 1$
Reflections collected / unique	1955 / 1616 [R (int) = 0.0303]
Completeness to 2theta = 27.10	99.7%
Refinement method	Full-matrix least-squares on F^2
Data/restraints / parameters	1616 / 1 / 137
Goodness-of-fit on F^2	0.929
Final R indices [I>2sigma (I)]	R1 = 0.0539, wR2 = 0.1374
R indices (all data)	R1 = 0.915, wR2 = 0.1624
Absolute structure parameter	-0.09 (19)
Extinction coefficient	0.000 (3)
Largest diff. peak and hole	0.203 and -0.185 $e.A^{-3}$

Table VIII. Bond Length [Å] and Angle [Deg] for 26j.

S(1) – C(2)	1.802(6)
S(1) – C(6)	1.808(7)
O(1) – C(4)	1.428(5)
C(2) – C(3)	1.530(8)
C(3) – C(4)	1.529(7)
C(4) – C(7)	1.525(7)
C(4) – C(5)	1.545(7)
C(5) – C(6)	1.530(7)
C(7) – C(12)	1.383(7)
C(7) – C(8)	1.406(7)
C(8) – C(9)	1.381(8)
C(9) – C(10)	1.401(9)
C(9) – C(14)	1.509(9)
C(10) – C(11)	1.372(9)
C(11) – C(12)	1.388(7)
C(11) – C(13)	1.510(9)
C(2) – S(1) – C(6)	98.2(3)
C(3) – C(2) – S(1)	111.1(4)
C(2) – C(3) – C(4)	114.5(4)
O(1) – C(4) – C(7)	111.4(4)
O(1) – C(4) – C(3)	104.7(4)
C(7) – C(4) – C(3)	111.3(4)
O(1) – C(4) – C(5)	109.1(3)
C(7) – C(4) – C(5)	108.4(4)
C(3) – C(4) – C(5)	111.9)4)
C(6) – C(5) – C(4)	114.2(4)
C(5) – C(6) – S(1)	110.9(4)
C(12) – C(7) – C(8)	118.3(5)
C(12) – C(7) – C(4)	121.5(4)
C(8) – C(7) – C(4)	120.3(4)
C(9) – C(8) – C(7)	120.9(5)
C(8) – C(9) – C(10)	119.0(5)
C(8) – C(9) – C(14)	120.5(6)
C(10) – C(9) – C(4)	120.5(6)
C(11) – C(10) – C(9)	120.9(5)
C(10) – C(11) – C(12)	119.2(6)
C(10) – C(11) – C(13)	121.3(6)
C(12) – C(11) – C(13)	119.4(6)
C(7) – C(12) – C(11)	121.6(5)

A selected member of the bicyclic alcohols was also a subject for structural study. For only the first time, an investigation was made of the conformational preferences of DNBCN-9-ols *via* single crystal X-ray diffraction analysis and by 1D and 2D NMR measurements in $DCCl_3$ utilizing $^{1}H/^{13}C$, Nuclear Overhauser Enhancement spectroscopy (NOESY). The latter showed the long-range through space coupling among the hydrogens. Gradient Heteronuclear Multiple Quantum Correlation Spectroscopy (gHMQC) indicated the direct coupling between protons and the corresponding carbons. Initially, the conformational preferences of alcohol **27a** were deduced from NOESY data and further corroborated by DQCOSY, which showed correlations among protons and Heteronuclear Multiple Bond Correlation (HMBC) experiments. The NOESY spectrum was best explained by assuming a CC conformation for **27a**. One set of configurational and conformational possibilities for **27a** in solution are shown (Figure 8).

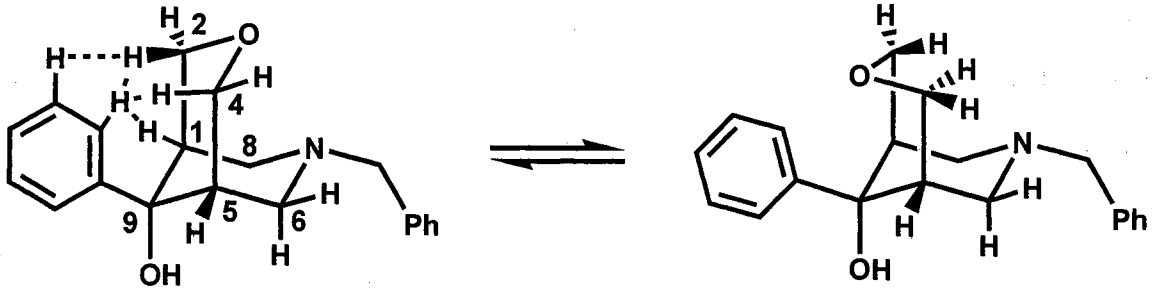


Figure 8. Conformational possibilities of **27a** in solution.

Initially, we elected to examine the ^{1}H spectrum of **27a** at 300 MHz. The spectrum (plate XXXVIII) showed 6 major peaks at δ 2.72-2.78 [m, 2 H, $H_{(1,5)}$], δ 3.31–3.36 [dd, 4 H, $H_{(6,8)}$], δ 3.56–3.66 [dd, 4 H, $H_{(2,4)}$], δ 3.60 [s, 2 H, H_2C-Ph], δ 4.75 [s, 1 H, OH], and δ

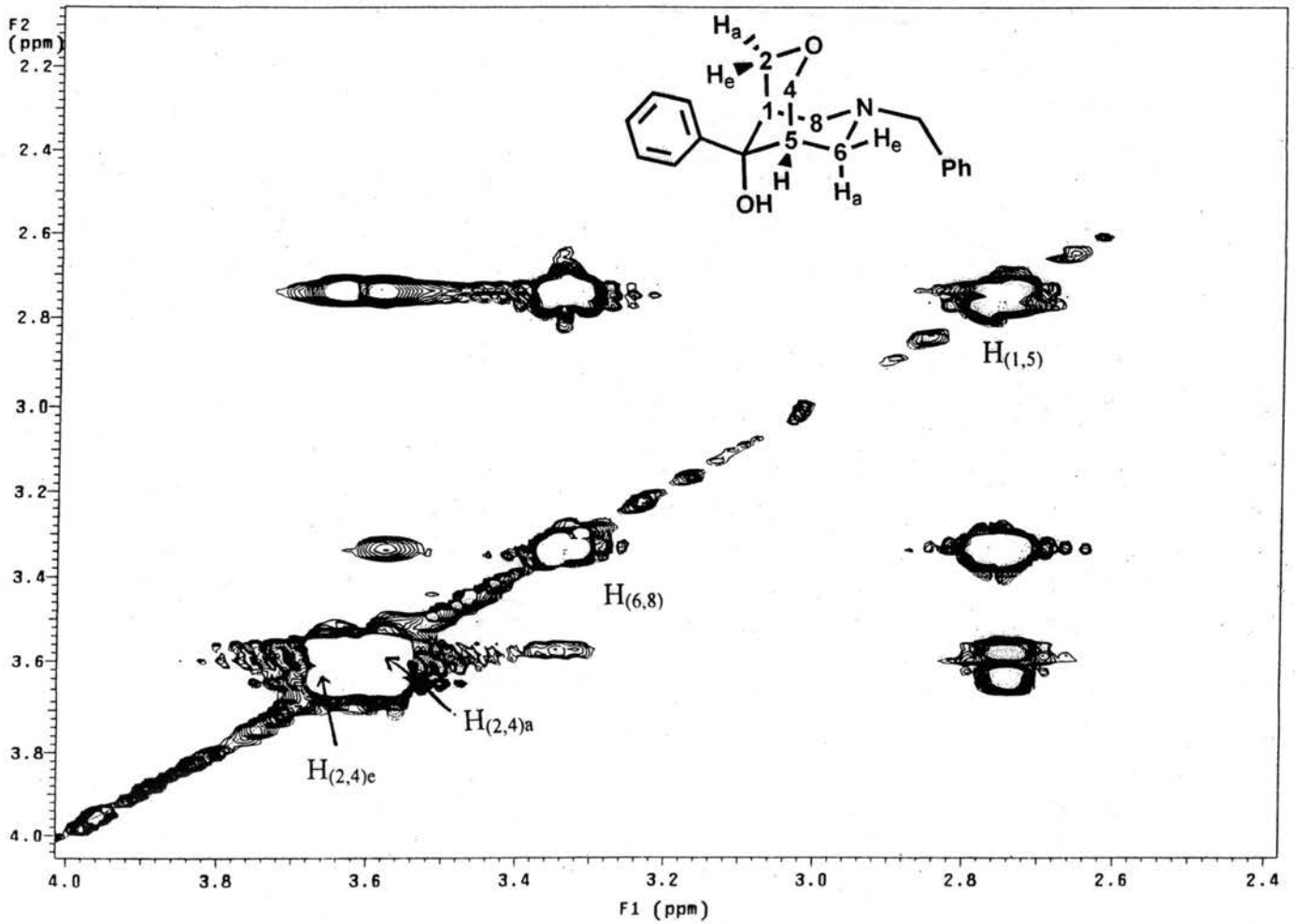
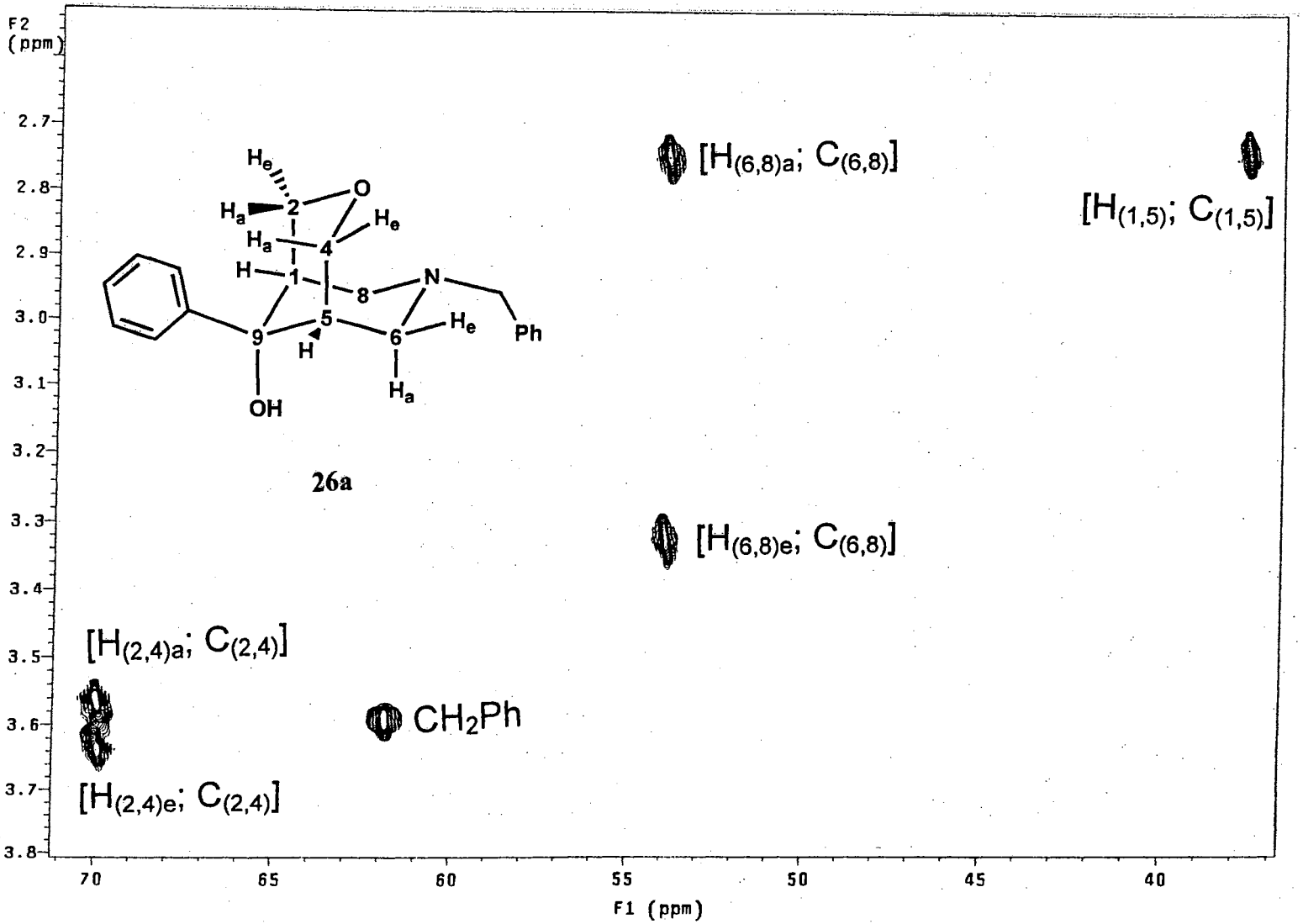


Figure 9. 2D COSY Spectrum of **27a** (without pyridine-d_5).

7.25–7.45 [m, 10 H, 2 Ar-*H*]. Both rings in each of the systems in equilibrium can be considered as having axial and equatorial positions. Therefore, one may expect to see 2 sets of peaks for $H_{(2,4)a}$ and $H_{(2,4)e}$ and 2 sets for $H_{(6,8)a}$ and $H_{(6,8)e}$. We obtained a 2D COSY (Figure 9) spectrum of **27a** and chose an entry point of δ 2.76 which corresponded to $H_{(1,5)}$ at the bridgeheads. Crosspeaks were observed for the coupling of $H_{(1,5)}$ with δ 3.34 of $H_{(6,8)e}$ or $H_{(6,8)a}$ and with δ 2.75 of $H_{(2,4)e}$ or $H_{(2,4)a}$. Since $H_{(2,4)ea}$ are closer to O, which has a larger electronegativity value than N, the signals should be in the region of higher frequency (downfield) than that of $H_{(6,8)ea}$. Generally, in a cyclohexyl ring the axial protons commonly appear more upfield than equatorial protons.[48] Therefore, the signal at δ 3.58 was attributed to $H_{(2,4)a}$ and that due to $H_{(2,4)e}$ was at δ 3.64. A crosspeak was also observed for the J geminal coupling between $H_{(2,4)e}$ and $H_{(2,4)a}$. The spectrum also showed that $H_{(6,8)}$ had only one signal at δ 3.34. There was, however, a crosspeak that connected this signal to $H_{(2,4)ea}$. This probably resulted from long range "W" coupling,[2e,43] which is good support for the expected CC conformation in **27a** product. A discussion for this will be clearer when pyridine-d_5 was added.

Like $H_{(2,4)ea}$, we also expected to see the separated signal from $H_{(6,8)e}$ and $H_{(6,8)a}$ in the 2D COSY spectrum of **27a**. Unfortunately, this was not possible since signals of axial and equatorial protons at C(6,8) overlapped (Figure 9). Another method was needed to determine if the signal at δ 3.34 was for $H_{(6,8)a}$ or $H_{(6,8)e}$. It was decided to obtain a 2D spectrum using HMQC. Unexpectedly, Figure 10 showed an extra signal at δ 2.76 for $H_{(1,5)}$, but correlated with the signal of $H_{(6,8)}$ at δ 3.33. This proved that the signal at δ 3.33 was for $H_{(6,8)e}$, and, hence, the signal at δ 2.76 was due to $H_{(6,8)a}$. This information also indicated that the signals of $H_{(6,8)a}$ and $H_{(1,5)}$ overlapped each other. Moreover, the



26a

Figure 10. 2D gHMQC Spectrum of **27a**.

signal for 2 H on H_2C-Ph was also displayed at δ 3.60 between the signals of $H_{(2,4)e}$ and $H_{(2,4)a}$ in the spectrum. The spectrum proved that the tall singlet peak at δ 3.60 in ^{1}H NMR was for H_2C-Ph. Again this signal was, unfortunately, buried under the $H_{(2,4)ea}$ region in the COSY spectrum (Figure 9).

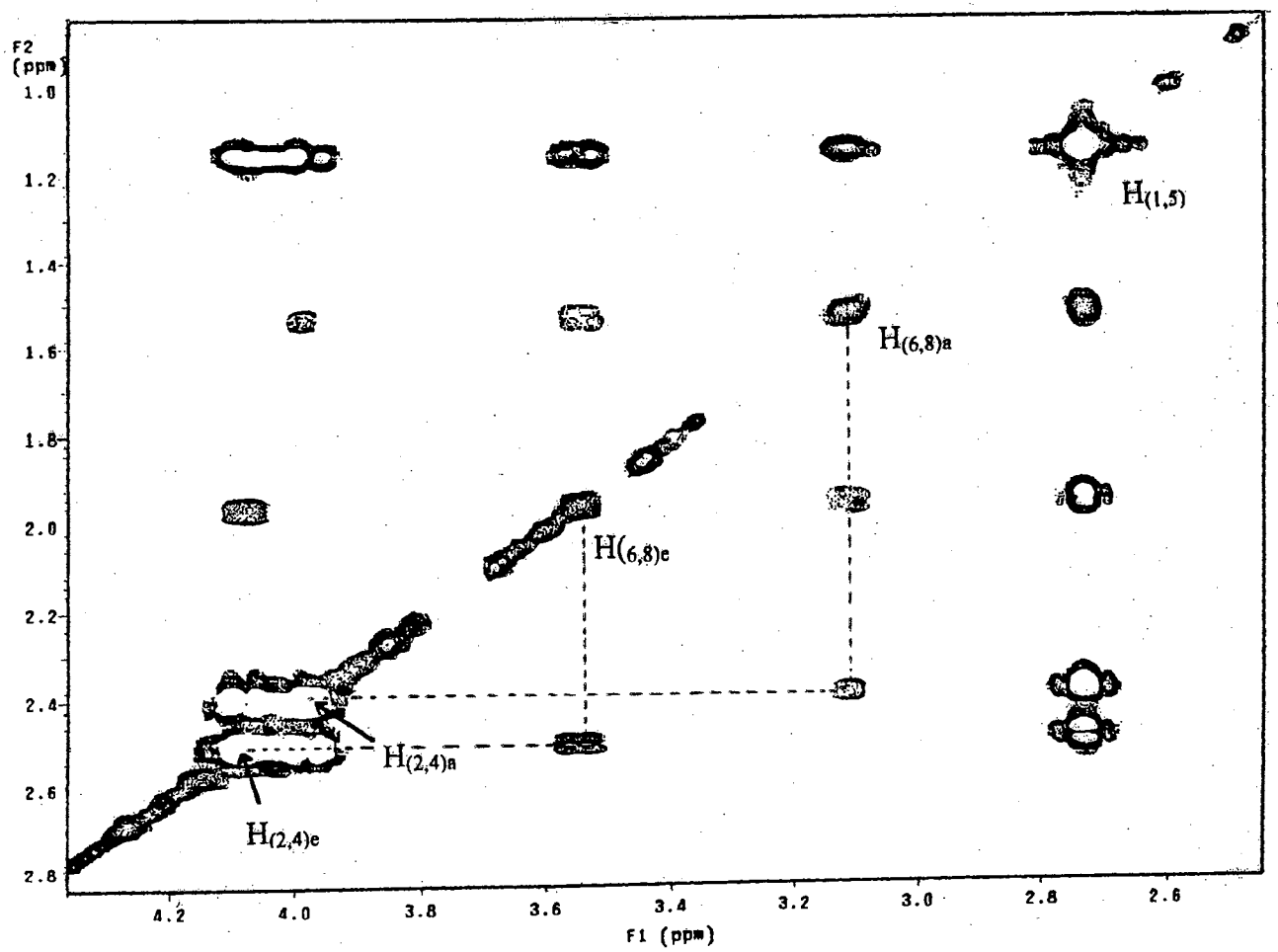
To clarify the matter, another solvent was added. Pyridine-d_5 is known as a solvent for ASIS, which stands for *A*romatic *S*olvent-*I*nduced *S*hift.[52] Upon adding pyridine-d_5, it was expected that all the signals for protons on the aromatic systems would be shifted to lower field. The new ^{1}H spectrum (plate XXXIX) beautifully separated out all the signals (Table IX) and showed the full spectrum of alcohol **27a**.

We again obtained and re-analyzed the 2D COSY (Figure 11) spectrum with greater resolution and sensitivity at 598.724 MHz. The spectrum showed the signals as more distinguishable with the addition of pyridine-d_5. In Figure 11, an entry point of $H_{(1,5)}$ at δ 2.72 was chosen. Crosspeaks were observed for these protons with signals at δ 3.05 [$H_{(6,8)a}$], δ 3.47 [$H_{(6,8)e}$], δ 3.89 [$H_{(2,4)a}$], and δ 4.04[$H_{(2,4)e}$]. A new crosspeak [compared

Table IX. ^{1}H chemical shifts (δ) and multiplicities of 27a in presence of Pyridine-d_5.

Proton	δ values (ppm)
$H_{(1,5)}$	2.54 (s)
$H_{(2,4)a}$	3.77-3.81 (dd)
$H_{(2,4)e}$	3.88-3.92 (d)
$H_{(6,8)a}$	2.90-2.93 (d)
$H_{(6,8)e}$	3.33-3.37 (dd)
H_2C-Ph	3.60 (s)
OH	4.75 (s)

s = singlet, d = doublet, dd = doublet-of-doublet.



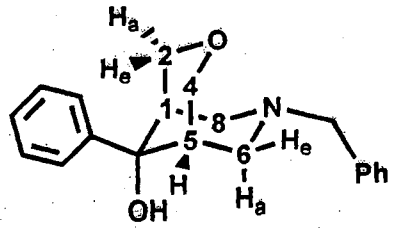


Figure 11. 2D COSY Spectrum of **27a** (with pyridine-d_5).

to the previous spectrum (Figure 9) before adding pyridine-d_5] for the geminal coupling between $H_{(6,8)a}$ and $H_{(6,8)e}$ was observed (Figure 11). Also seen was a new signal for H_2C-Ph at δ 3.82. Furthermore, the new COSY spectrum (Figure 11) of **27a** also clearly showed crosspeaks which displayed the long range "W" pattern (4 bond coupling).[2e,43] The dominant, 4-bond coupling is between $H_{(6,8)a}$ and $H_{(2,4)a}$ as a "W" pattern. This "W" type coupling is believed to occur when the tails of the orbitals of the first and fourth bond overlap.[43] This is only possible when both rings are in chair conformations in the CC form. The "W" pattern of 4-bond coupling is shown using thick bonds (Figure 12).

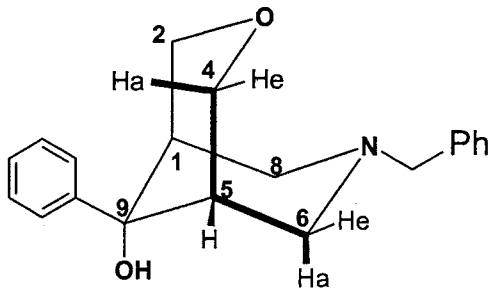


Figure 12. "W" arrangement in **27a**.

To assure that the CC conformations were present in the bicyclic alcohol **27a**, a 2D NMR NOESY experiment (Figure 13) was performed and showed the through-space coupling of protons. If the NOESY spectrum showed the through-space coupling between $H_{(2,4)a}$ and signals in the aromatic region, then the CC form was supported . As expected, Figure 13 showed the crosspeaks of $H_{(2,4)a}$ with signals in the aromatic region, and, moreover, with signals for the $H_{(1,5)}$ and signals in aromatic region. The through-space coupling is only possible in the CC form of **27a** (as the dotted lines show in Figures 8 and 13) while it is not possible in a BC conformer for **27a**. This, indeed, proved that

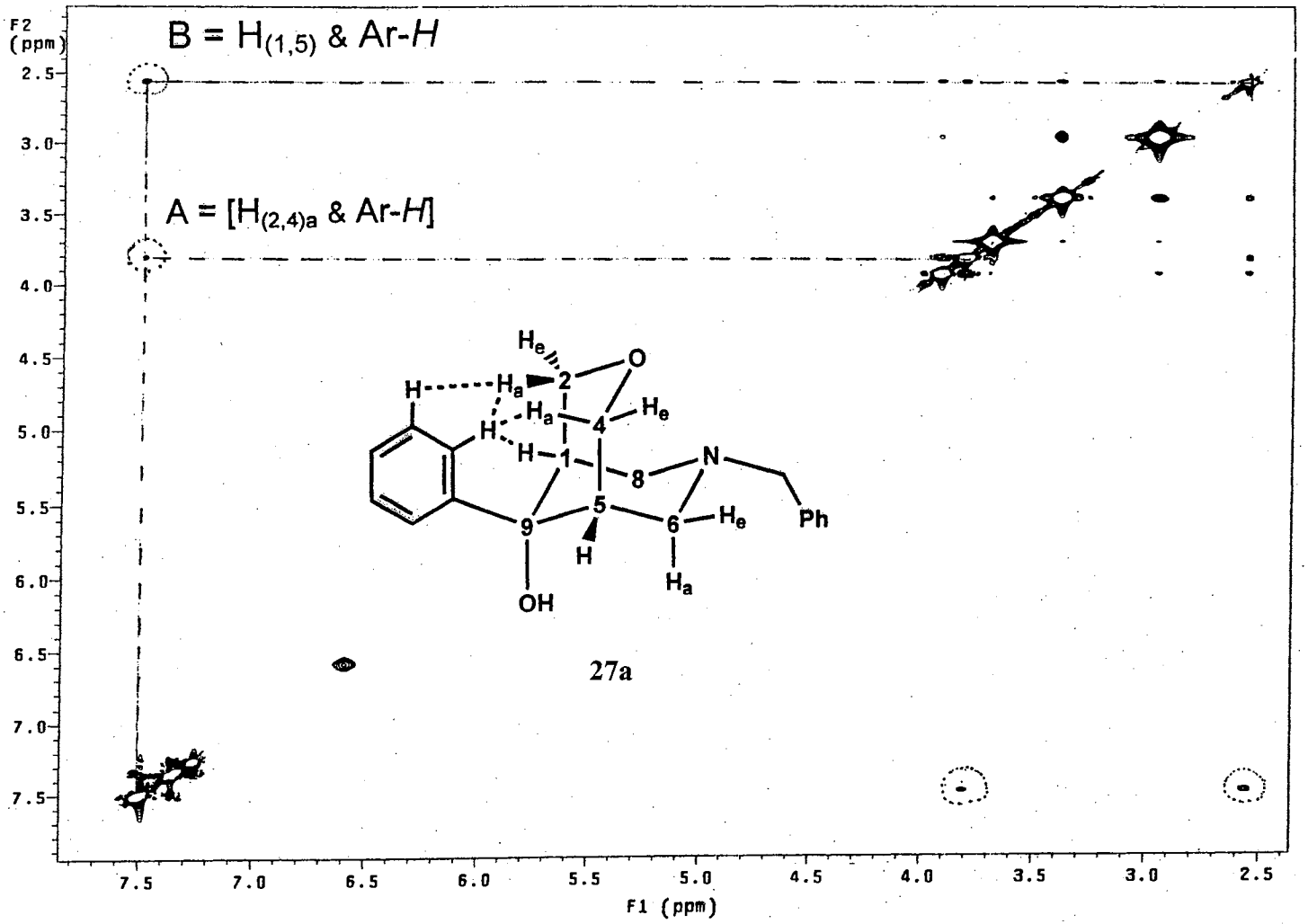


Figure 13. 2D NOESY Spectrum of **27a**.

both rings of **27a** are in chair conformations (CC form) on the average in $DCCl_3$ at room temperature.

For the sake of completeness, an X-ray diffraction analysis was performed on a single crystal of alcohol **27a**. The X-ray data (Figure 14) demonstrated that the bicyclic system in the tertiary alcohol **27a** was the CC form. The crystal was monoclinic (Table X). The elemental analysis suggested that there is one molecule of water trapped within the crystal of **27a**. The X-ray diagram of **27a** confirmed that a water molecule formed a weak hydrogen bond between hydrogen atom of the OH group and the unshared electron pair of the nitrogen atom.

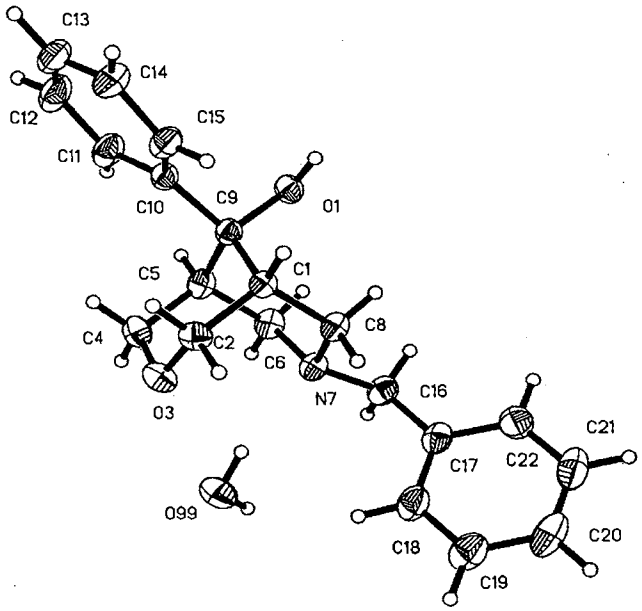


Figure 14. The crystal structure of **27a**.

Table X. Crystal Data and Structure Refinement for 27a.

Empirical formula	$C_{20}H_{25}NO_3$
Formula weight	327.41
Temperature	293 (2) K
Wavelength	0.71073 Å
Crystal System, space group	Monoclinic, $P_2(1)/C$
Unit cell dimensions	a = 7.664 (2) Å $\alpha = 90°$
	b = 10.652 (2) Å $\beta = 97.370°$ (10)
	c = 21.229 (3) Å $\gamma = 90°$
Volume	1718.8 (6) $Å^3$
Z, Calculated density	4, 1.265 Mg/m^3
Absorption coefficient	0.084 mm^{-1}
F (000)	704
Completeness to 2theta = 26.37	94.4%
Theta range for data collection	1.93° to 26.37°
Index ranges	$-1 \leq h \leq 9$, $-13 \leq k \leq 1$, $-26 \leq l \leq 26$
Reflections to 2theta = 26.37	4790 / 3518 [R(int) = 0.0277]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3518 / 0 / 218
Goodness-of-fit on F^2	1.052
Final R indices [I>2sigma (I)]	R1 = 0.0592, wR2 = 0.1570
R indices (all data)	R1 = 0.0991, wR2 = 0.1833
Extinction coefficient	0.006 (2)
Largest diff. Peak and hole	0.227 and – 0.315 $e.Å^{-3}$

As mentioned earlier, the 1,2-addition to **21** of selected aryl Grignard reagents unexpectedly resulted in a new conformation in the bicyclic alcohol produced. Analysis

of a single crystal of alcohol **28**, for example, confirmed the tertiary bicyclic alcohol was a CB form with the sulfur-containing ring in a chair and the nitrogen-containing ring in a boat (Figures 15 and 16). Such a dramatic change in the conformations might be explained as follows. The sulfur atom is big (covalent radius is 1.02 Å compared to 0.73 Å for O and 0.77 Å for C). The high temperature and a big, bulky aryl Grignard reagent may force attack on C(9) of ketone **21b** opposite from the N atom. Such attachment may

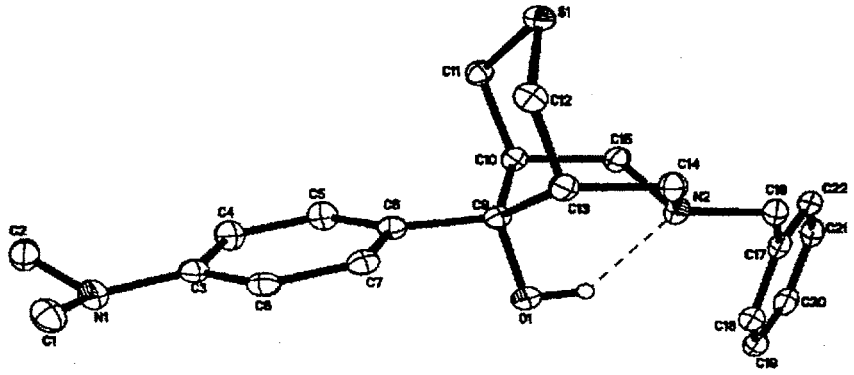
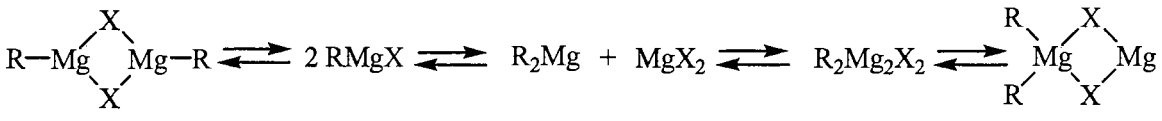


Figure 15. Perspective view of **28**.

flip the sulfur end toward the nitrogen end. The flipping of the sulfur end may result in repulsion between unshared electrons on sulfur and nitrogen. The repulsion may force the nitrogen end to bend down. A unit cell of **28** is illustrated in Figure 16.

The solvent is a significant factor affecting the composition of Grignard reagent in solution.[61] In solution, a Grignard reagent is not the simple monomeric species RMgX. Instead, the term Grignard reagent normally refers to a Schlenk equilibrium.[56] It has been



32 **33** **34** **35** **36**

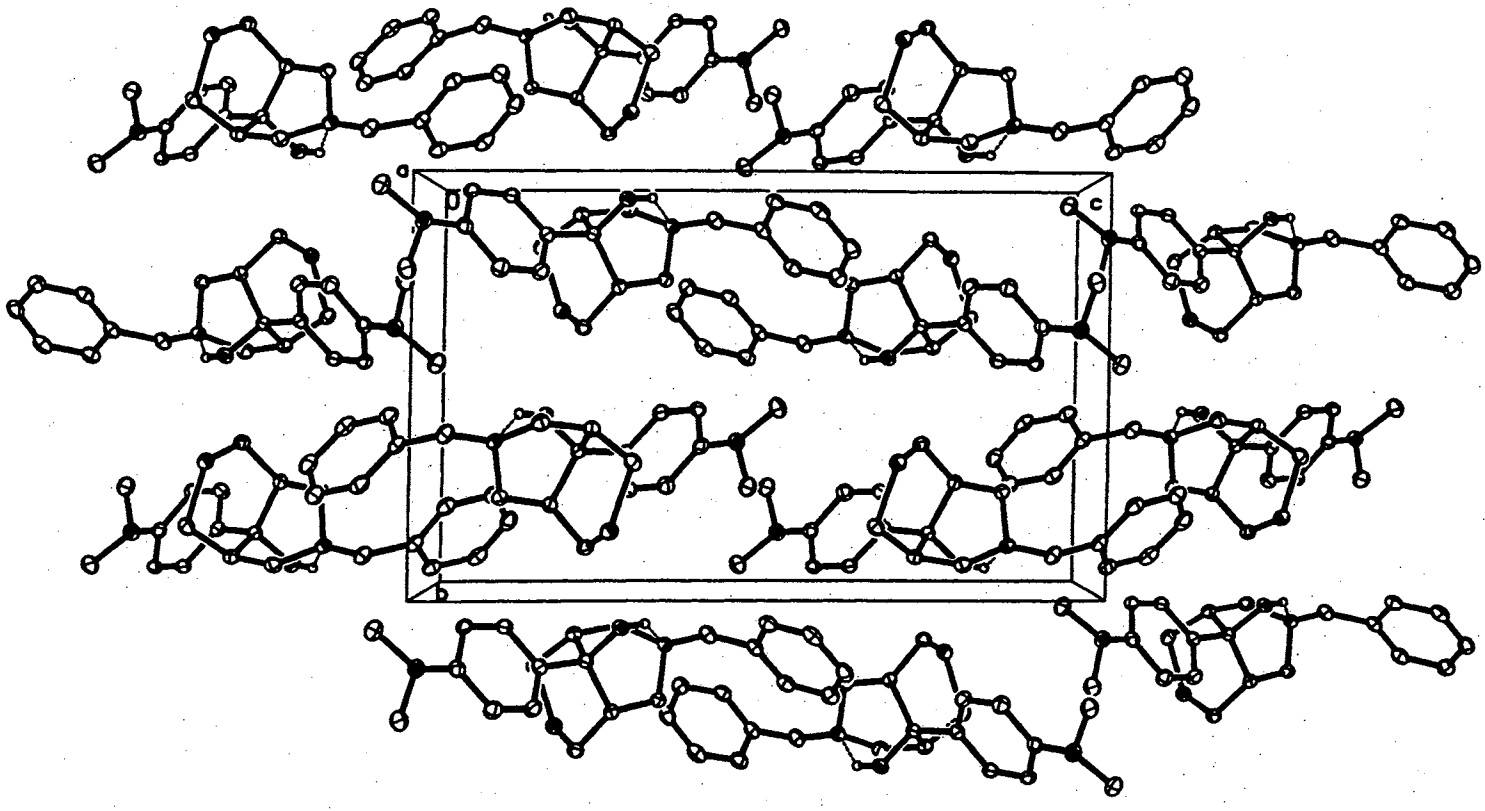


Figure 16. A Crystalline Unit Cell of **28b**.

suggested that monomeric species (**33-34**) of a Grignard reagent are present in THF.[8] Monomeric species in a 1,2-carbonyl addition predominantly attack equatorially to form the axial alcohol product.[3,32,61,65] Thus, the dominant effects in the attack on **21b** and in the flipping of the rings in **28** may be associated with the solvation of Grignard reagent species in the THF solution of ketone **21b** and/or in the aggregation of monomeric species of the Grignard reagent. In addition, the temperature also plays a significant role on the composition of Grignard reagents in solution.[61] Changing solution temperatures can significantly alter the solubility of the components of Grignard reagents.[67] It appears that low temperatures can shift the monomer-dimer equilibrium toward the dimeric arylmagnesium complex in THF, and at high temperature, Grignard reagents in THF are often monomeric.[46] Since the production of **28** was performed under reflux, 4-*N,N*-dimethylaminophenylmagnesium bromide reagent in THF is likely monomeric. Possibly, this could lead to a flipping of the sulfur-containing ring perhaps through interaction with the N atom and RMgX. The intramolecular hydrogen bonding (Table XI) between the hydrogen atom of the hydroxyl group and the unshared electron pair of the nitrogen is an additional stabilization factor which may be necessary to accomplish the conformational transition from a CC into a CB form in alcohol **28**. The aid of intramolecular hydrogen bonding in stabilizing certain structures, especially in the DHBCN family, has been recently reported.[11] Crystal data for **28** is in Table XIII.

Table XI. Intermolecular Hydrogen Bonds for 28 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...N(2)	0.87	1.88	2.6139(14)	141.5

Table XII. Crystal Data and Structure Refinement for 28.

Mol. Formula	$C_{22}H_{28}N_2OS$
MWT	368.52
Temperature	100 (2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, P2(1)2(1)2(1)
Cell dimensions	a = 9.1781(6) Å $\alpha = 90°$
	b =11.1062(8) Å $\beta = 90°$
	c = 18.3868(13) Å $\gamma = 90°$
Volume	1874.2(2) $Å^3$
Z,Calculated density	4, 1.306 Mg/m^3
Absorption Coefficient	0.187 mm^{-1}
F (000)	792
Crystal size	0.36 x 0.16 x 0.10 mm^3
Theta range for data collection	2.14° to 27.50°
Index ranges	$-11 \leq h \leq 11, -14 \leq k \leq 14, -23 \leq l \leq 23$
Reflections collected / unique	16383 / 4293 [R (int) = 0.0193]
Completeness to 2theta = 27.50°	99.7%
Absorption correction	Semi-empirical from equivalents
Max. and Min. transmission	0.9816 and 0.9359
Refinement method	Full-matrix least-squares on F^2
Data/restraints / parameters	4293 / 0 / 237
Goodness-of-fit on F^2	1.045
Final R indices [I>2sigma (I)]	R1 = 0.0271, wR2 = 0.0713
R indices (all data)	R1 = 0.0276, wR2 = 0.0716
Absolute structure parameter	0.01 (5)
Largest diff. peak and hole	0.312 and -0.168 e. $Å^{-3}$

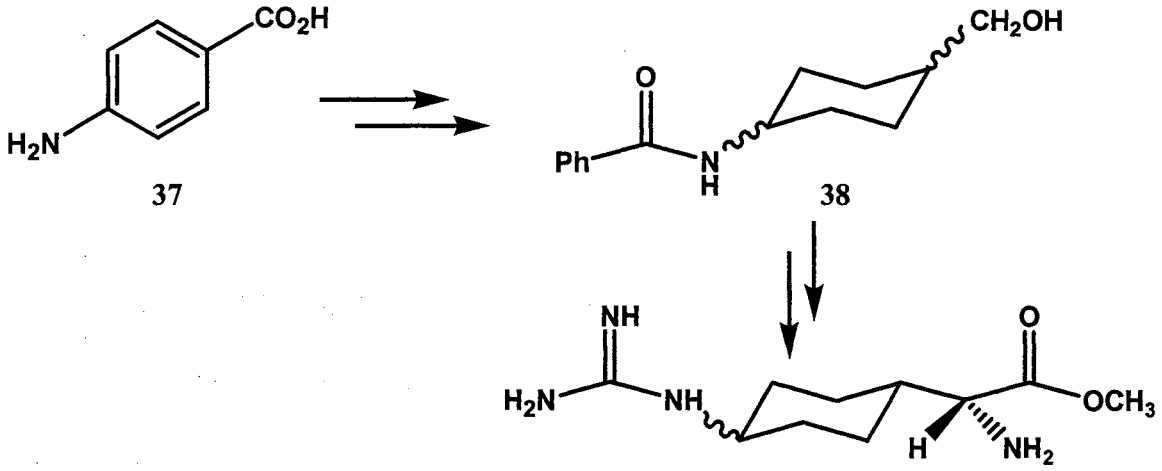
SUMMARY

Methodology was developed and utilized for the production and characterization of a series of new and novel pyranols, thiopyranols, and 3,7-DHBCN-9-ols. Conformational preferences of pyranols, thiopyranols [model systems] and some 3,7-DHBCN-9-ols were investigated by low-temperature, 1D, and 2D NMR spectroscopy. Low-temperature and gHMQC NMR experiments on the simple alcohol **26j** suggested the prevalence of a flattened chair form with an aryl group in a pseudo-equatorial position. The COSY, NOESY, and gHMQC experiments suggested the prevalence of a CC form for one 3,7-DHBCN-9-ol **27a** containing an oxygen atom in a ring as part of a bicyclic system, while a CB form was confirmed for one 3,7-DHBCN-9-ol **28** containing a sulfur atom in a ring as part of a bicyclic system. Selected systems were subjected to X-ray analysis to confirm the configurations. The research study also showed that the solvents (diethyl ether vs. THF) and temperature played significant role in 1,2-addition of organometallic reagents to the carbonyl group of 3,7-DHBCN family.

Although the alcohols produced have not yet been tested for their analgesic and multi-class antiarrhythmic activities, it is expected that biological studies of these agents could provide valuable information for the invention of potentially effective analgesic and multi-class antiarrhythmic agents possessing high activity and relatively low toxicity.

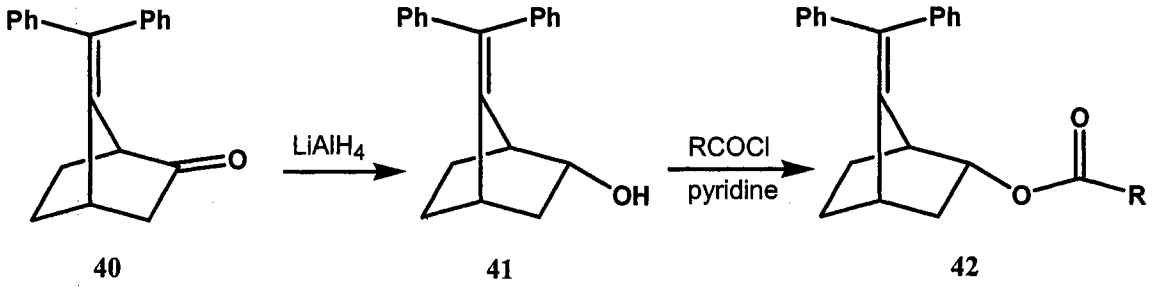
NEXT GENERATION: THE DERIVATIVES OF 3,7-DHBCN-9-OLS

Certain derivatives of alcohols, especially esters[6,41,42] and carbamates,[14,17] have been recorded as useful in treatment of arrhythmias. Banfi's research group reported[6] the potential antiarrhythmic activity in rat of ester analog **39** of D-arginine. The reaction



started with the conversion of 4-aminobenzoic acid (**37**) to alcohol **38**. The conversion of alcohol **38**, *via* several steps, gave **39** as a mixture of *cis* (D-**39**) and *trans* (L-**39**) isomers, respectively. Preliminary pharmacological results[6] showed the *trans* isomer L-**39** had higher antiarrhythmic activity then *cis* D-**39** isomer.

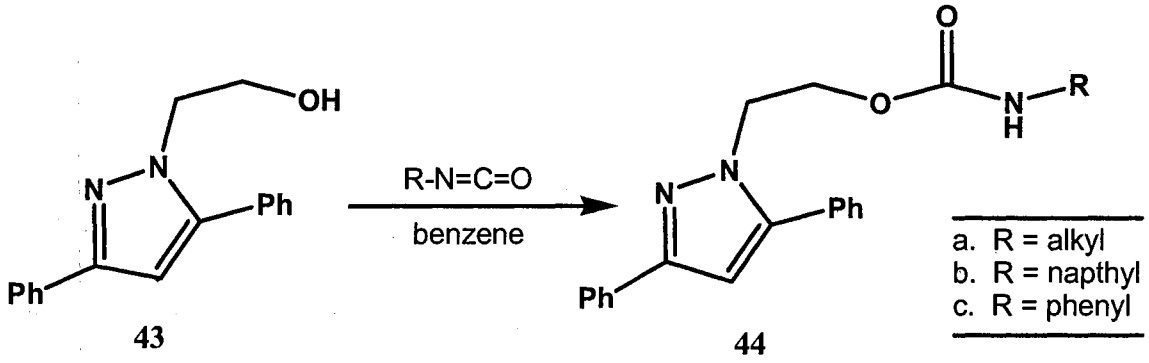
The esterification of alcohols was also included in work of Longobardi and co-workers.[41] Treatment of ketone **40** with $LiAlH_4$ yielded alcohol **41**. Alcohol **41** was subjected to acylation with selected aliphatic and aromatic acyl chloride in pyridine solution to afford **42**. The biological examinations of esters **42** showed an appreciable antiarrhythmic activity in rats, as well as local anesthetic activity in rats and mice.[41]



40 41 42

a. R = CH_3
b. R = $CH(CH_3)_2$
c. R = C_3H_5
d. R = C_6H_{11}

Carbamates are often useful biological agents.[14,17] Investigations by the Bondavalli's research group[14] reported the synthesis of carbamate derivatives **44** from reaction of alcohol **43** with corresponding isocyanates. The biological study showed that carbamates **44** possessed remarkable depressant, antiarrhythmic, and analgesic activities in mice and rats as well as a weak platelet antiaggregating activity in vitro.[14]

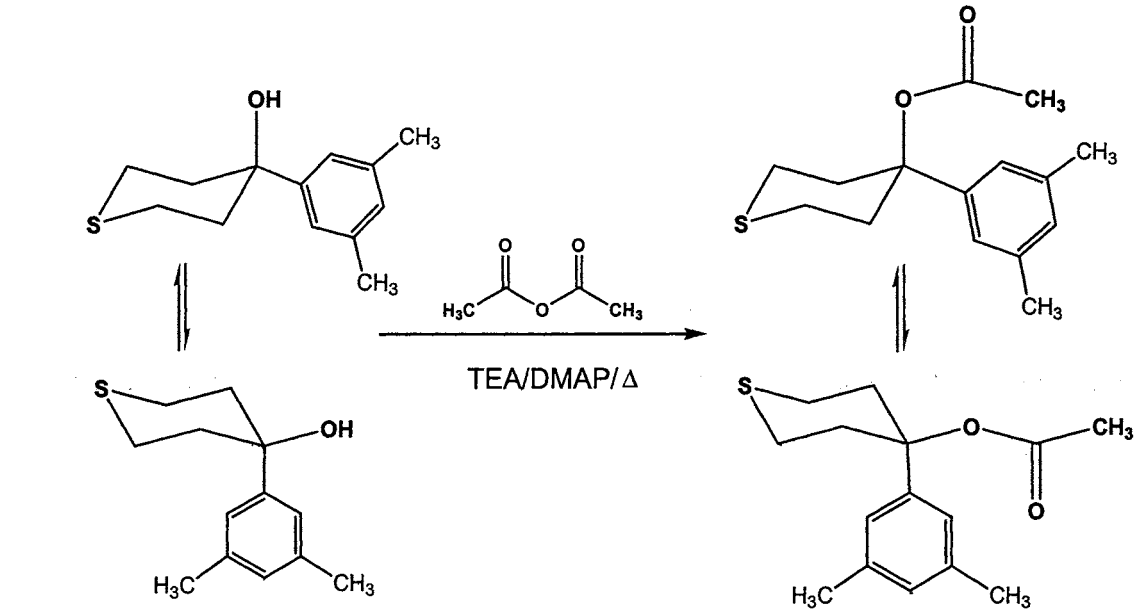


43 44

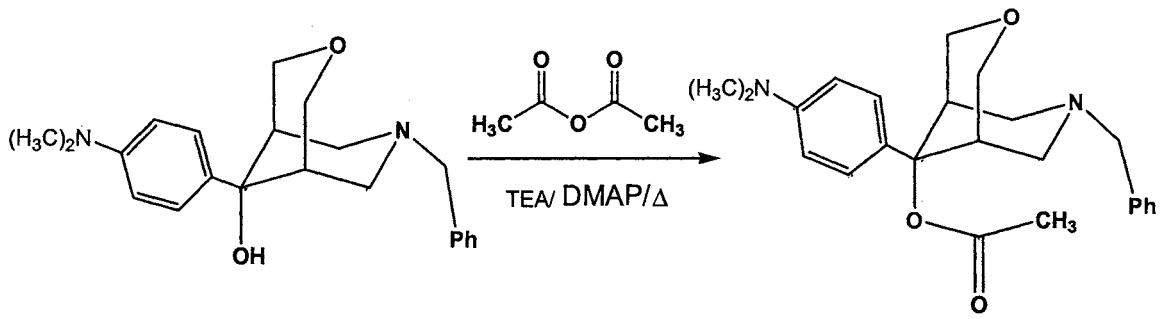
a. R = alkyl
b. R = napthyl
c. R = phenyl

Derivatives of tertiary monocyclic alcohols **26**, and bicyclic alcohols **27** and **28** have not been extensively investigated. Based upon solid biological rationale of esters and carbamates, as medicinal agents, derivatives of alcohols **26j** and **27** are reasonable targets. Such derivatives (**26j'** and **27b'**) can reasonably be expected to significantly possess the multi-class antiarrhythmic activity. Moreover, esters and carbamates can serve as the hydroxyl and amino protecting groups, which can be cleaved *in vivo* to re-

generate precursors **26j-27b**. As discussed in Chapter I, the introduction of a weak polar group at C(9) of the 3,7-DHBCN family [see compound **18** (Table IV)] can induce good antiarrhythmic activity.



26j **26j'**



27b **27b'**

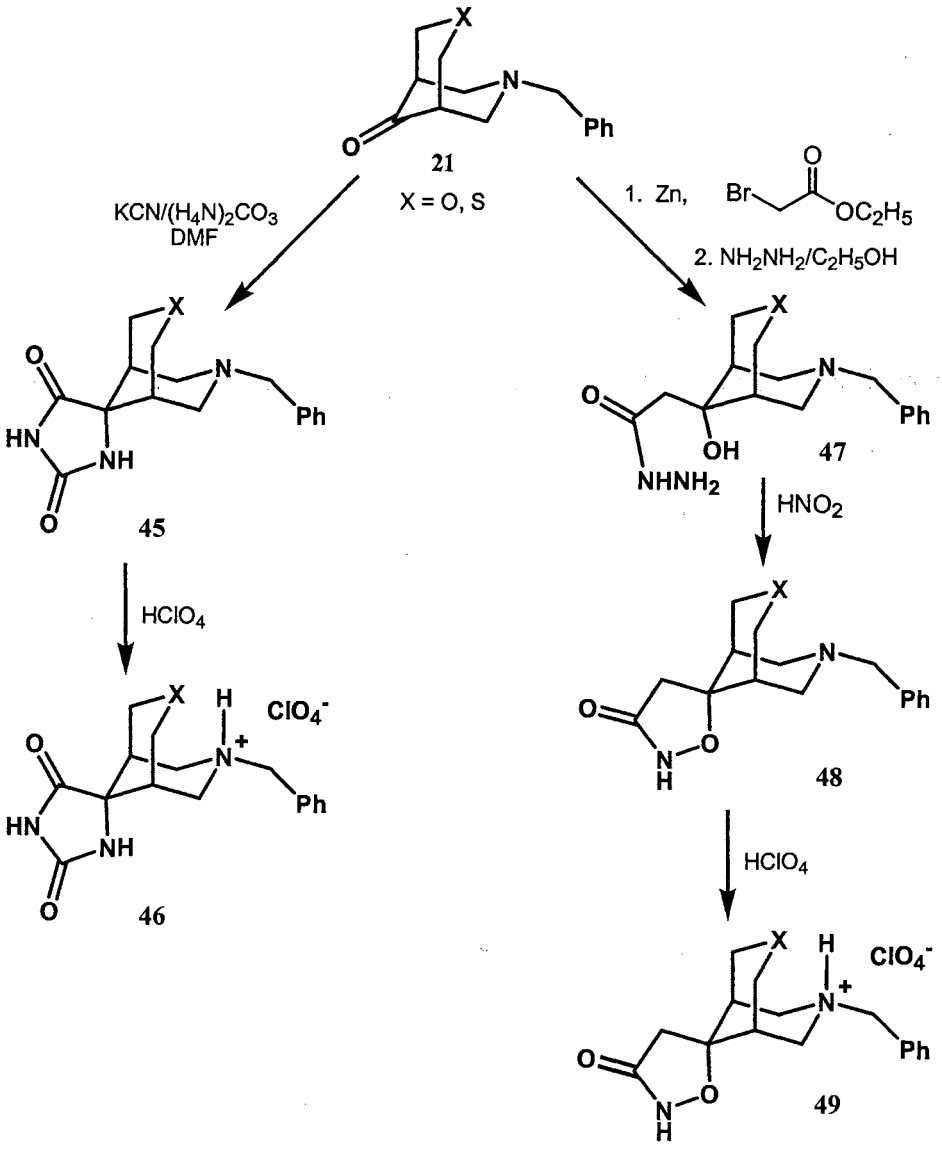
Alcohol **26j** was subjected to a first attempt. Treatment the alcohols **26j** with acetic anhydrides (Ac_2O) in triethylamine (TEA) and an equimolar amount of 4-dimethylaminopyridine (DMAP) gave highly pure crystals of ester **26j'** in a good yield (75.6%). DMAP served as a catalyst in this transesterification. It has been reported[75] that DMAP was a powerful catalysts in acyl transfer reactions of tertiary alcohols,

superior to pyridine and other tertiary amines. Reactions can proceed well without purification. However, an attempt to convert a bicyclic alcohol **27b** to ester **27b'** using the same conditions as with **26j'** failed, and starting alcohol **27b** was recovered. At this time the only reasonable explanation is due to the extreme steric hindrance of the bicyclic alcohol **27b** that creates difficulty for the hydroxyl group to react with either acetic anhydride alone or with the acetylpyridinium ion.

SUGGESTIONS FOR FUTURE WORK

As found in earlier works, several 3,7-DHBCN derivatives exhibited antiarrhythmic activity in more than one class action. An ideal drug would have a slight class I and dominant class II, III, and/or IV features. For instance, tedisamil (**23**), with a cyclopentyl group at C(9), was found to have a predominant class III action (prolongation of APD, and the refractory period) with slight class I action.[7,26] An important structural feature of most class II agents is the presence of a hydroxyl group.[70] Class III and IV actions of salts of DHBCNs possibly originate from the perchlorate anion and certain functional groups like NO_2, imidazole, SO_2, and NH_3^+.[70] Based upon such a rationale, it is proposed that derivatives **45-49** could display class I, III, and IV action. Other five-membered rings attached to C(9) may have antiarrhythmic properties. Oxazolidinone has been reported as antibacterial[38] and/or antimicrobial[30] agents while imidazolidinones were useful as anticancer,[33] antifungal, and/or antibacterial[24] agents. However, the effects of isoxazolidinone, and imidazolidinone on antiarrhythmic activity of 3,7-DHBCNs have not been examined. Thus, it might be worthwhile to test such effects of compounds **45-49**. Agents **46** and **49** may have better activity than their parents **45** and **48** since salts **46**

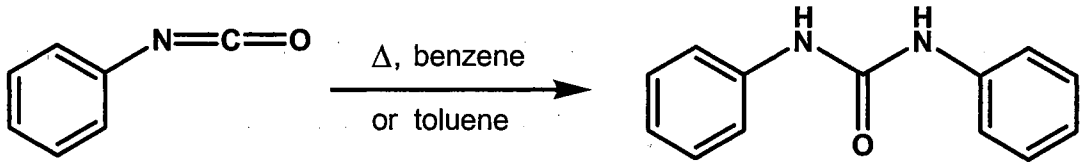
and **49** dissolve in water more easily than **45** and **48**. Previous studies have reported perchlorate salts of the 3,7-DHBCN family have better multi-class antiarrhythmic activity in comparison to their parent compounds in dog models. [2,5,11,15,24]



NEW METHODOLOGY

In attempting to convert alcohols such as **26** to carbamates using phenylisocyanate, an unusual self condensation of phenylisocyanate to *N,N'*-diphenylurea was discovered.[18]

Since *N,N'*-diphenylurea is not available in our lab for a relate research study, we used this new method to determine conversion amounts. Ureas constitute a family of organic molecules of great interest.[7] *N,N'*-Diphenylurea (**51**, carbanilide) is widely used in numerous applications.[8-10,13,14,16,19] Consequently, the synthesis of **51** has been the subject of several studies[1,2,4-6,11,12,15] utilizing a variety of solvents and metallic inorganic catalysts. However, these methods requires a large excess of solvents, long reaction times, tedious work-ups, and elaborate purification procedures. Since **51** is relatively



50 **51**

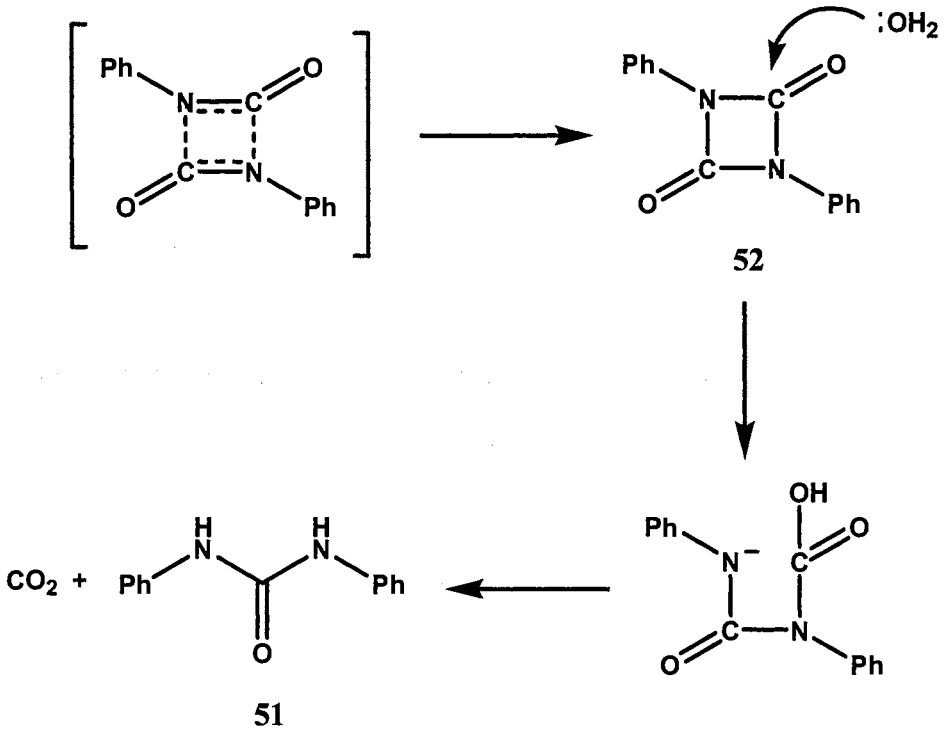
expensive, a new simplified, inexpensive and clean approach to prepare **51** from phenyl isocyanate (**50**) in anhydrous benzene or toluene was of interest.[18] The approach was attractive because of its operational simplicity and the high yield of very pure product obtained without recrystallization. Moreover, no catalyst was required, and the reaction time was short. Table XX below contains pertinent results which were the

Table XIII. Self-condensation of Phenyl Isocyanate (50) in Benzene and Toluene.

Solvent	Yield (%)	mp (°C)
Benzene	62	239-240, *lit*[7] mp 238-240 °C
Toluene	62	241.5-242

average of two separate experiments. It is possible that the glassware and/or solvents, and/or nitrogen contained sufficient water to allow for the conversion to the urea. However, an intermediate like **52** could form prior to decomposition of the reaction

mixture. During the aqueous wash of the reaction mixture, water could attack **52** with generation of **51** and CO_2 as illustrated. Formation of **52** is conceivable at the boiling point of the solvent utilized.



CHAPTER III

EXPERIMENTAL SECTION

General Information: Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and were uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin-Elmer 2000 FTIR as liquid films or KBr pellets. All ^{1}H and ^{13}C NMR spectra were taken either on a Varian Unity Gemini 300 MHz spectrometer operating at 300.082 MHz and 75.463 MHz, respectively, or on a Varian Unity Inova 600 MHz spectrometer operating at 598.724 MHz and 150.57 MHz, respectively. Chemical shifts for the ^{1}H and ^{13}C spectra were recorded ($DCCl_3$, in the case of **27a** a few drops of pyridine-d_5 was added) in δ or ppm values downfield from TMS [$(CH_3)_4Si$]. All 2D NMR experiments for simple alcohol **26j** were recorded on the Varian Unity Inova 400 MHz spectrometer operating at 399.905 MHz. All 2D NMR experiments for bicyclic alcohol **27a**, including COSY, NOESY, HMQC, and HMBC, were recorded on the Varian Unity Inova 600 MHz spectrometer operating at 598.724 MHz.

Syntheses were performed under an atmosphere of N_2 with magnetic stirring unless otherwise specified. ACS grade solvents were used after drying with molecular sieves (3A and/or 4A) and sodium before executing most reactions. All chromatographic separations were performed via a flash column using "Baker" silica gel (40 μm mesh) as the stationary phase. Glassware was oven-dried overnight and flushed with N_2 before each reaction.

The following chemical and reagents were obtained commercially and used without further purification: benzylamine (Aldrich), paraformaldehyde (Aldrich), glacial acetic acid and hydrochloric acid [37%] (Spectrum Chemical), potassium hydroxide pellets [KOH, 85%] and ammonium chloride [NH_4Cl] (EM Science), potassium carbonate [K_2CO_3, 100%] (J.T.-Baker), Norit A 'Decolorizing Carbon' (Pfanstiehl Chemical Co., Waukegan, IL), tetrahydro-4*H*-pyran-4-one (Aldrich), and tetrahydrothiopyran-4-one (Aldrich). Grignard reagents were either purchased from Aldrich [phenyl-, *p*-chlorophenyl-, *p*-tolyl-, *p*-tert-butylphenylmagnesium bromide] or from Rieke Metal [4-*N,N*-dimethylphenyl-, 3,5-dimethylphenylmagnesium bromide], 1001 Kingbird Rd., Lincoln, NE 68521, and used without further purification. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

Part A: The Preparation of monocyclic alcohols as model systems.

*Note the single apostrophe on a carbon is for carbons in the benzene ring (*N-CH_2-C_6H_5*).*

4-Phenyltetrahydropyran-4-ol (26a): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 36 mL (0.108 mol, 3 *M*) of phenylmagnesium bromide in dry ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydro-4*H*-pyran-4-one (**25a**, 5.0 g, 0.050 mol) in anhydrous ether (35 mL) was added dropwise to the Grignard reagent. A slightly exothermic reaction occurred with gentle reflux as an ether solution of **25a** was added to the Grignard reagent. Upon applying heat (≈ 0.5 h) with stirring, the mixture partially solidified, and thus additional dry ether (30 mL) was added dropwise. After another 0.5 h, the mixture turned cream colored. Heating was discontinued, but stirring was

maintained until the flask cooled to RT. To the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 120 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified via flash column chromatography (ether:hexanes, 1:1) to give **26a** as colorless crystals (7.83 g, 0.044 mol, 88%), mp 100.0-100.5 °C. IR 3337 (O-H), 780/687 (mono) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.98 [s, 1 H, OH], 1.68-1.74 [m, 2 H, $H_{(3,5)a}$], 2.15-2.25 [m, 2 H, $H_{(3,5)e}$], 3.86-3.91 [m, 2 H, $H_{(2,6)a}$], 3.93-4.01 [m, 2 H, $H_{(2,6)e}$], 7.30-7.35 [m, 2 H, $H_{(2',6')}$], 7.40-7.45 [m, 2 H, $H_{(3',5')}$], 7.52-7.55 [m, 1 H, $H_{(4')}$]; ^{13}C NMR ppm 38.57 [$C_{(3,5)}$], 63.74 [$C_{(2,6)}$], 70.38 [$C_{(4)}$], 124.38 [$C_{(3',5')}$], 127.09 [$C_{(2',6')}$], 128.35 [$C_{(4')}$], 148.04 [$C_{(1')}$]. *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.89; H, 8.05.

4-(4-Chlorophenyl)tetrahydropyran-4-ol (26b): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 100 mL (0.100 mol, 1 *M*) of *para*-chlorophenylmagnesium bromide in dry ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydro-*4H*-pyran-4-one (**25a**, 5.0 g, 0.050 mol) in anhydrous ether (35 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, heat was discontinued, but stirring was maintained overnight at RT. To the milky mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 200 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified by flash column chromatography (ether:hexanes, 1:1) to give **26b** as colorless crystals (9.96 g,

0.047 mol, 94%), mp 77-78 °C. IR 3393 (O-H), 828 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 2.41 [s, 1 H, OH], 1.59-1.64 [m, 2 H, $H_{(3,5)a}$], 2.02-2.12 [m, 2 H, $H_{(3,5)e}$], 3.76-3.82 [m, 2 H, $H_{(2,6)a}$], 3.83-3.92 [m, 2 H, $H_{(2,6)e}$], 7.30-7.33 [m, 2 H, $H_{(2',6')}$], 7.38-7.41 [m, 2 H, $H_{(3',5')}$]; ^{13}C NMR ($DCCl_3$) ppm 38.47 [$C_{(3,5)}$], 63.57 [$C_{(2,6)}$], 70.05 [$C_{(4)}$], 125.94 [$C_{(3',5')}$], 128.40 [$C_{(2',6')}$], 132.78 [$C_{(4')}$], 146.64 [$C_{(1')}$]. *Anal.* Calcd for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16; Cl, 16.67. Found: C, 62.37; H, 6.14, Cl, 16.71.

4-(4-*N,N*-Dimethylaminophenyl)tetrahydropyran-4-ol (26c): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 200 mL (0.100 mol, 0.5 *M*) of *N,N*-dimethylaminophenylmagnesium bromide in THF, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydro-4*H*-pyran-4-one (**25a**, 5.0 g, 0.050 mol) in anhydrous THF (35 mL) was added dropwise to the Grignard reagent. Upon applying heat (≈ 1 h), the mixture became a white solid. An additional 30 mL of anhydrous THF was added. After another 1.5 h at gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. To the new cream-colored mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 150 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a brown solid, which was purified via flash column chromatography (ethyl acetate:hexanes, 1:1) to give **26c** as colorless crystals (8.50 g, 0.038 mol, 77%), mp 102-103 °C. IR 3437 (O-H), 817 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.91 [s, 1 H, OH], 2.95 [s, 3 H, CH_3], 1.68-1.70 [m, 2 H, $H_{(3,5)a}$], 2.08-2.13 [m, 2 H, $H_{(3,5)e}$], 3.80-3.82 [m, 2 H, $H_{(2,6)a}$], 3.88-3.92 [m, 2 H, $H_{(2,6)e}$], 6.72-6.73 [d, 2 H, $H_{(3',5')}$], 7.33-7.35 [d, 2 H, $H_{(2',6')}$];

^{13}C NMR ($DCCl_3$) ppm 26.98 [$C_{(3,5)}$], 38.65 [CH_3], 40.45 [$C_{(2,6)}$], 69.81 [$C_{(4)}$], 112.30 [$C_{(3',5')}$], 118.42 [$C_{(1')}$], 125.21 [$C_{(2',6')}$], 149.54 [$C_{(4')}$]. *Anal.* Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.73; H, 8.66; N, 6.21.

4-(3,5-Dimethylphenyl)tetrahydropyran-4-ol (26d): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 200 mL (0.100 mol, 0.5 *M*) of 3,5-dimethylphenylmagnesium bromide in THF, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydro-4*H*-pyran-4-one (**25a**, 5.0 g, 0.050 mol) in anhydrous THF (35 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, the mixture turned to a light yellow solid, which was redissolved in additional dry ether (50 mL). After another 3 h at gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 170 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified via flash column chromatography (ether:hexanes, 1:1) to give **26d** as colorless crystals (7.56 g, 0.037 mol, 73.5%), mp 102-103 °C. IR 3387 (O-H) cm^{-1}. ^{1}H NMR ($DCCl_3$) δ 2.05 [s, 1 H, OH], 2.35 [s, 3 H, CH_3], 1.62-1.64 [m, 2 H, $H_{(3,5)a}$], 2.10-2.15 [m, 2 H, $H_{(3,5)e}$], 3.81-3.84 [m, 2 H, $H_{(2,6)a}$], 3.88-3.92 [m, 2 H, $H_{(2,6)e}$], 6.92 [s, 1 H, $H_{(4')}$], 7.08 [s, 2 H, $H_{(2',6')}$]; ^{13}C NMR ($DCCl_3$) ppm 21.41 [CH_3], 38.66 [$C_{(3,5)}$], 63.79 [$C_{(2,6)}$], 70.31 [$C_{(4)}$], 122.18 [$C_{(2',6')}$], 128.69 [$C_{(4')}$], 137.82 [$C_{(3',5')}$], 148.11 [$C_{(1')}$]. *Anal.* Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.69; H, 8.80.

4-*p*-Tolyltetrahydropyran-4-ol (26e): A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 10 mL (0.01 mol, 1 *M*) of *p*-tolylmagnesium bromide in diethyl ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydro-4*H*-pyran-4-one (**25a**, 0.5 g, 0.050 mol, Aldrich) in anhydrous THF (25 mL) was added dropwise to the Grignard reagent. Upon applying heat (approximately 0.5 h), the light orange colored mixture turned copper in color. After 2 h at gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. Into the new mixture was added dropwise, with stirring and with a cooling ice bath (≈. 0 °C), 15 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 50 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of solvent gave a white solid, which was washed with cold petroleum ether. Recrystallization of white solid [petroleum ether:ether, 1:1] gave colorless crystals of **26e** (0.712 g, 0.0037 mol, 74%), mp 105-105.5 °C. IR 3378 (O-H), 833 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.86 [s, 1 H, OH], 1.63-1.64 [m, 2 H, $H_{(3,5)a}$], 2.08-2.19 [m, 2 H, $H_{(3,5)e}$], 2.34 [s, 3 H, CH_3], 3.80-3.86 [m, 2 H, $H_{(2,6)a}$], 3.87-3.96 [m, 2 H, $H_{(2,6)e}$], 7.16-7.19 [d, 2 H, $H_{(3',5')}$], 7.35-7.36 [d, 2 H, $H_{(2',6')}$]; ^{13}C NMR ($DCCl_3$) ppm 20.91 [CH_3], 38.74 [$C_{(3,5)}$], 63.87 [$C_{(2,6)}$], 70.38 [$C_{(4)}$], 124.32 [$C_{(2',6')}$], 129.10 [$C_{(3',5')}$], 136.87 [$C_{(1')}$], 145.12 [$C_{(4')}$]. *Anal.* Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.42.

4-(4-*t*-Butylphenyl)tetrahydropyran-4-ol (26f): A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 4.99

mL (0.00499 mol, 2 *M*) of 4-*t*-butylphenylmagnesium bromide in diethyl ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydropyran-4*H*-4-one (**25a**, 0.5 g, 0.00499 mol) in anhydrous THF (20 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. Into the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 15 mL of aq NH_4Cl (20%). After 1 h, the mixture was extracted with dry ether (3 x 50 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of solvent gave a white solid, which was washed with cold petroleum ether. Recrystallization of the white solid [petroleum ether:ether, 1:1] gave colorless crystals of **26f** (0.737 g, 0.0033 mol, 67%), mp 185.5-186 °C. IR 3372 (O-H), 823 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.33 [s, 3 H, CH_3], 1.65 [s, 1 H, OH], 1.68-1.73 [m, 2 H, $H_{(3,5)a}$], 2.12-2.23 [m, 2 H, $H_{(3,5)e}$], 3.84-3.89 [m, 2 H, $H_{(2,6)a}$], 3.90-3.98 [m, 2 H, $H_{(2,6)e}$], 7.25-7.26 [d, 2 H, $H_{(2',6')}$], 7.41-7.42 [d, 2 H, $H_{(3',5')}$]; ^{13}C NMR ($DCCl_3$) ppm 31.28 [CH_3], 34.41 [$C(CH_3)_3$], 38.72 [$C_{(3,5)}$], 63.91 [$C_{(2,6)}$], 70.44 [$C_{(4)}$], 124.11 [$C_{(3',5')}$], 125.37 [$C_{(2',6')}$], 144.98 [$C_{(1')}$], 150.18 [$C_{(4')}$]. *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.93; H, 9.67.

4-Phenyltetrahydrothiopyran-4-ol (26g): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 29 mL (0.099 mol, 3 M) of phenylmagnesium bromide in diethyl ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydrothiopyran-4-one (**25b**, 5.0 g, 0.043 mol) in anhydrous ether (35 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, the mixture solution turned milky. Heating was discontinued,

but stirring was maintained overnight at RT. To the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 100 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified via flash column chromatography (ether:hexanes, 1:1) to give **26g** as colorless crystals (6.04 g, 0.031 mol, 72%) (Lit[9,19] 58%), mp 76-77 °C (Lit[9,19] 76-78 °C). *The compound has been recorded, but no IR and NMR data were reported.*[9,18] IR 3337 (O-H), 762/701 (mono) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.63 [s, 1 H, OH], 1.98-2.03 [m, 2 H, $H_{(3,5)a}$], 2.13-2.23 [m, 2 H, $H_{(3,5)e}$], 2.43-2.48 [m, 2 H, $H_{(2,6)a}$], 3.16-3.25 [m, 2 H, $H_{(2,6)e}$], 7.27-7.49 [m, 5 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 24.08 [$C_{(2,6)}$], 39.42 [$C_{(3,5)}$], 71.79 [$C_{(4)}$], 124.15 [$C_{(4')}$], 127.02 [$C_{(2',6')}$], 128.35 [$C_{(3',5')}$], 148.93 [$C_{(1')}$].

4-(4-Chlorophenyl)tetrahydrothiopyran-4-ol (26h): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 86 mL (0.086 mol, 1 M) of *para*-chlorophenylmagnesium bromide in diethyl ether, and stirred at RT under N_2 for 5 min. A solution of tetrahydrothiopyran-4-one (**25b**, 5.0 g, 0.043 mol) in anhydrous ether (35 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, the mixture turned solid, and another 30 mL of dry THF was added. Heating was discontinued after 2 h, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 200 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified via flash column chromatography (ethyl

acetate:hexanes, 1:1) to give **26h** as colorless crystals (8.89 g, 0.039 mol, 91%), mp 86-87 °C. IR 3409 (O-H), 862 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.75 [s, 1 H, OH], 1.94-1.99 [m, 2 H, $H_{(3,5)a}$], 2.08-2.18 [m, 2 H, $H_{(3,5)e}$], 2.42-2.47 [m, 2 H, $H_{(2,6)a}$], 312-3.22 [m, 2 H, $H_{(2,6)e}$], 7.30-7.33 [m, 2 H, $H_{(2',6')a}$], 7.38-7.41 [m, 2 H, $H_{(2',6')e}$]; ^{13}C NMR ($DCCl_3$) ppm 23.96 [$C_{(2',6')}$], 39.33 [$C_{(3,5)}$], 71.61 [$C_{(4)}$], 125.74 [$C_{(3',5')}$], 128.40 [$C_{(2',6')}$], 132.77 [$C_{(4')}$], 147.45 [$C_{(1')}$]. *Anal.* Calcd for $C_{11}H_{13}ClOS$: C, 57.76; H, 5.73; S, 14.02. Found: C, 57.86; H, 5.71; S, 13.75.

4-(4-*N,N*-Dimethylaminophenyl)tetrahydrothiopyran-4-ol (26i): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 172 mL (0.086 mol, 0.5 M) of *N,N*-dimethylaminophenylmagnesium bromide in THF, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydrothiopyran-4-one (**25b**, 5.0 g, 0.043 mol) in anhydrous THF (35 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, the mixture turned to a white solid, which was redissolved in 30 mL of anhydrous THF. Heating was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 150 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified via flash column chromatography (ethyl acetate:hexanes, 1:3) to give **26i** as colorless crystals (7.13 g, 0.030 mol, 70%), mp 110.5-112 °C. IR 3402 (O-H), 813 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.62 [s, 1 H, OH], 2.93 [s, 3 H, CH_3], 1.97-2.03 [m, 2 H, $H_{(3,5)a}$], 2.08-2.18 [m, 2 H, $H_{(3,5)e}$], 2.42-2.46 [m, 2 H, $H_{(2,6)a}$], 3.11-3.20 [m, 2 H, $H_{(2,6)e}$], 6.70-6.73 [d, 2 H,

$H_{(3',5')}$], 7.30-7.33 [d, 2 H, $H_{(2',6')}$]; ^{13}C NMR ($DCCl_3$) ppm 24.34 [$C_{(2,6)}$], 39.60 [$C_{(3,5)}$], 40.52 [CH_3], 71.19 [$C_{(4)}$], 112.31 [$C_{(3',5')}$], 125.05 [$C_{(1')}$], 125.99 [$C_{(2',6')}$], 149.54 [$C_{(4')}$]. *Anal.* Calcd for $C_{13}H_{19}NOS$: C, 65.78; H, 8.07; N, 5.90. Found: C, 65.86; H, 8.09; N, 5.82.

4-(3,5-Dimethylphenyl)tetrahydrothiopyran-4-ol (26j): A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet, and a glass stopper. The flask was charged with 172 mL (0.086 mol, 0.5 M) of 3,5-dimethylphenylmagnesium bromide in THF, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydrothiopyran-4-one (**25b**, 5.0 g, 0.043 mol) in anhydrous THF (35 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, the mixture partially solidified, and additional dry THF (30 mL) was added. Heat was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 150 mL of aq NH_4Cl (20%). After 0.5 h, the mixture was extracted with dry ether (3 x 100 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a white solid, which was purified via flash column chromatography (ethyl acetate:hexanes, 1:1) to give **26j** as colorless crystals (7.16 g, 0.032 mol, 75%), mp 76-77.5 °C. IR 3402 (O-H) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.61 [s, 1 H, OH], 2.32 [s, 3 H, CH_3], 1.95-2.00 [m, 2 H, $H_{(3,5)a}$], 2.11-2.20 [m, 2 H, $H_{(3,5)e}$], 2.42-2.46 [m, 2 H, $H_{(2,6)a}$], 3.14-3.24 [m, 2 H, $H_{(2,6)e}$], 6.91 [s, 1 H, $H_{(4')}$], 7.07 [s, 2 H, $H_{(2',6')}$]; ^{13}C NMR ($DCCl_3$) ppm 21.44 [CH_3], 24.17 [$C_{(3,5)}$], 39.54 [$C_{(2,6)}$], 71.75 [$C_{(4)}$], 121.98 [$C_{(2',6')}$], 128.64 [$C_{(4')}$], 137.90 [$C_{(3',5')}$], 149.05 [$C_{(1')}$]. *Anal.* Calcd for $C_{13}H_{18}OS$: C, 70.22; H, 8.16. Found: C, 70.19; H, 8.22.

4-*p*-Tolyltetrahydrothiopyran-4-ol (26k): A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 8.60 mL (0.0086 mol, 1 *M*) of *p*-tolylmagnesium bromide in diethyl ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydrothiopyran-4-one (**25b**, 0.5 g, 0.0043 mol) in anhydrous ether (20 mL) was added dropwise to the Grignard reagent. After 1 h at gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. Into the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 15 mL of aq NH_4Cl (20%). After 1 h, the mixture was extracted with dry ether (3 x 50 mL), and the combined extracts were dried (K_2CO_3) overnight. Upon standing at RT (10-12 h), the slow evaporation of solvent yielded colorless crystals of **26k** (0.618 g, 0.0030 mol, 69%), mp 74-74.5 °C. IR 3413 (O-H), 817 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.53 [s, 1 H, OH], 1.98-2.03 [m, 2 H, $H_{(3,5)a}$], 2.13-2.22 [m, 2 H, $H_{(3,5)e}$], 2.34 [s, 3 H, CH_3], 2.44-2.49 [m, 2 H, $H_{(2,6)a}$], 3.15-3.25 [m, 2 H, $H_{(2,6)e}$], 7.16-7.19 [d, 2 H, $H_{(3',5')}$], 7.34-7.37 [d, 2 H, $H_{(2',6')}$]; ^{13}C NMR ($DCCl_3$) ppm 20.88 [CH_3], 24.19 [$C_{(2,6)}$], 39.55 [$C_{(3,5)}$], 71.64 [$C_{(4)}$], 124.11 [$C_{(2',6')}$], 129.05 [$C_{(3',5')}$], 136.70 [$C_{(4')}$], 146.13 [$C_{(1')}$]. *Anal.* Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.20; H, 7.93.

4-(4-*t*-Butylphenyl)tetrahydrothiopyran-4-ol (26l): A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 4.3 mL (0.0043 mol, 2 *M*) of 4-*t*-butylphenylmagnesium bromide in diethyl ether, and the mixture was stirred at RT under N_2 for 5 min. A solution of tetrahydrothiopyran-4-one

(**25b**, 0.5 g, 0.0043 mol) in anhydrous ether (20 mL) was added dropwise to the Grignard reagent. After 1 h of gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. Into the new mixture was added dropwise, with stirring and with a cooling ice bath (≈ 0 °C), 15 mL of aq NH_4Cl (20%). After 1 h, the mixture was extracted with dry ether (3 x 50 mL), and the combined extracts were dried (K_2CO_3) overnight. Evaporation of the solvent gave a light yellow solid, which was washed with cold petroleum ether. Recrystallization of a white solid [ether:petroleum ether, 1:1] gave colorless crystals of **26l** (0.673 g, 0.0030 mol, 68%), mp 143-143.5 °C. IR 3413 (O-H), 823 (para) cm^{-1}. ^1H NMR ($DCCl_3$) δ 1.32 [s, 3 H, C*H*$_3$], 1.52 [s, 1 H, OH], 2.00-2.05 [m, 2 H, $H_{(3,5)a}$], 2.13-2.23 [m, 2 H, $H_{(3,5)e}$], 2.45-2.49 [m, 2 H, $H_{(2,6)a}$], 3.17-3.25 [m, 2H, $H_{(2,6)e}$], 7.36-7.42 [m, Ar-*H*] ; ^{13}C NMR ($DCCl_3$) ppm 24.26 [$C_{(2,6)}$], 31.31 [*C*H$_3$], 34.42 [*C*(CH$_3$)$_3$], 39.59 [$C_{(3,5)}$], 71.64 [$C_{(4)}$], 123.94 [$C_{(3',5')}$], 125.35 [$C_{(2',6')}$], 146.02 [$C_{(1')}$], 150.03 [$C_{(4')}$]. *Anal.* Calcd for $C_{15}H_{22}OS$: C, 71.95; H, 8.86. Found: C, 71.89; H, 8.93.

Part B: The Preparation of Bicyclic Alcohols.

*Note the single apostrophe on a carbon is for carbons in the benzene ring (*N-CH$_2$-*C$_6$H$_5$) while a double apostrophe signifies aryl carbon atoms in aryl ring connected to C(9) of the bicyclic ring.*

7-Benzyl-9-phenyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (27a). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 2.16 mL (6.48 mmol, 3 *M*) of phenylmagnesium bromide in diethyl ether, and the contents were stirred at RT under N_2 for 5 min. The solution of ketone **21a** (0.5 g, 0.002 mol) in anhydrous ether (35 mL) was added dropwise to the Grignard reagent in the flask.

After 1 h of gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with a cooling ice bath (≈ 0 °C), 20 mL of H_2SO_4 (9 *M*) with stirring. After 1 h, the water layer was separated and made basic *via* the addition of KOH pellets with a cooling ice bath. Dilution of this mixture was achieved with 100 mL of distilled water. The mixture was extracted with dry ether (3 x 50 mL) and dried (KOH) overnight. The mixture was filtered and treated dropwise with $HClO_4$ (60%), with stirring, which resulted in the formation of a white precipitate, which was then washed with cold ether and recrystallized (ethanol). The crystals were redissolved in 50 mL of distilled water, and the solution was made basic with NaOH (pH ≈ 12). Extraction was with the anhydrous ether (3 x 50 mL), and the combined extracts were dried (Na_2SO_4) overnight. Evaporation of the solvent yielded a final product **27a** (0.24 g, 0.78 mmol, 48%) as a white solid which was recrystallized (methanol), mp 91-92 °C. IR (film) 3344 cm^{-1} (O-H). ^1H NMR ($DCCl_3$ without pyridine-d_5) δ 2.72-2.78 [m, 2 H, $H_{(1,5)}$], 3.31–3.36 [dd, 4 H, $H_{(6,8)}$], 3.56–3.66 [dd, 4 H, $H_{(2,4)}$], 3.60 [s, 2 H, H_2C-Ph], 4.75 [s, 1 H, OH], and 7.25–7.45 [m, 10 H, 2 Ar-*H*]. ^1H NMR ($DCCl_3$ + few drops of pyridine-d_5) δ 2.57 [s, 1 H, $H_{(1,5)}$]; 2.91-2.93 [d,2 H, $H_{(6,8)a}$]; 3.36-3.38 [dd, 2 H, $H_{(6,8)e}$]; 3.68 [s, 2 H, CH_2]; 3.79-3.82 [d, 2 H, $H_{(2,4)a}$]; 3.89-3.92 [dd, 2 H, $H_{(2,4)e}$]; 6.59 [s, 1 H, OH]; 7.19-7.59 [m, 8 H, 2 Ar-*H*]. ^{13}C NMR ($DCCl_3$ + few drops of pyridine-d_5) 37.5 [$C_{(2,4)}$]; 52.8 [$C_{(1,5)}$]; 61.7 [$C_{(6,8)}$]; 69.7 [CH_2]; 72.3 [$C_{(9)}$]; 125.41 [$C_{(4'')}$]; 126.72 [$C_{(4')}$]; 127.85 [$C_{(3'',5'')}$]; 128.09 [$C_{(3',5')}$]; 128.55 [$C_{(2'',6'')}$]; 128.99 [$C_{(2',6')}$]; 138.90 [$C_{(1')}$]; 142.46 [$C_{(1'')}$]. *Anal.* Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. *Anal.* Calcd for $C_{20}H_{23}NO_2 \cdot H_2O$: C, 73.36; H, 7.69; N, 4.27. Found: C, 73.54, 73.41; H,

7.80, 7.69; N, 4.33, 4.33. In view of the presence of a water molecule, two separate analyses were obtained.

7-Benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (27b). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 18 mL (0.0085 mol, 0.5 *M*) of 4-*N,N*-dimethylaminophenylmagnesium bromide in THF, and the contents were stirred at RT under N_2 for 5 min. The solution of ketone **21a** (1.0 g, 0.0043 mmol) in anhydrous THF (25 mL) was added dropwise (for 0.5 h) to the Grignard reagent and stirred at RT under N_2 for 10 min. Upon applying heat (approximately 1 h), the light yellow solution turned copper color. After heating for 24 h at gentle reflux, heating was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with a cooling ice bath, 39 mL of aq. NH_4Cl (10%) and 6.4 mL of H_2SO_4 (9 *M*) with stirring. After 1 h, the mixture was made basic *via* the addition of KOH pellets (pH ≈ 12) with a cooling ice bath (≈ 0 °C). The mixture was extracted with dry ether (4 x 50 mL), and the combined extracts were dried (Na_2SO_4) overnight. The solution was mixed with decolorized charcoal (Norit A) and filtered through a celite pad. Evaporation of the solvent gave a brown solid which was stirred in petroleum ether (3 x 30 mL), each for 0.5 h. The petroleum ether was discarded. Evaporation of the solvent and recrystallization of the brown solid [denatured alcohol 3A:ether, 4:1] yielded a final product as colorless, crystals of **27b** (0.33 g, 45 %), mp 155-156 °C; IR (film) 3383 (O-H) cm^{-1}. ^1H NMR ($DCCl_3$) δ 2.38 [s, 2 H, $H_{(1,5)}$]; 2.46-2.50 [d, 2 H, $H_{(6,8)a}$]; 2.86-2.89 [dd, 2 H, $H_{(6,8)e}$]; 2.98 [s, 6 H, $N(CH_3)_2$]; 3.31 [s, 2 H, CH_2]; 3.96-3.99 [d, 2 H, $H_{(2,4)a}$]; 4.46-4.50 [dd, 2 H,

$H_{(2,4)e}$]; 4.75 [s, 1 H, OH]; 6.73-7.30 [m, 4 H, Ar-*H*]. ^{13} C NMR ($DCCl_3$) ppm 38.29 [$C_{(2,4)}$]; 40.41 [$N(CH_3)_2$]; 55.74 [$C_{(1,5)}$]; 62.31 [$C_{(6,8)}$]; 67.73 [CH_2]; 71.63 [$C_{(9)}$]; 112.50 [$C_{(3'',5'')}$]; 126.40 [$C_{(4')}$]; 126.63 [$C_{(3',5')}$]; 128.10 [$C_{(2',6')}$]; 128.52 [$C_{(2'',6'')}$]; 130.10 [$C_{(1'')}$]; 139.27 [$C_{(1')}$]; 149.90 [$C_{(4'')}$]. *Anal.* Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 74.83; H, 8.15; N, 8.06.

7-Benzyl-9-(4-*tert*-butylphenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (27c). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 3.24 mL (0.0065 mol, 2 *M*) of 4-*tert*-butylphenylmagnesium bromide in diethyl ether, and the contents were stirred at RT under N_2 for 5 min. A solution of ketone **21a** (0.5 g, 0.0022 mol) in anhydrous THF (5 mL) was added dropwise to the Grignard reagent in the flask over 0.5 min. Upon applying heat for 1 h, the light yellow mixture turned to brown and then to a clear orange liquid. After 60 h at reflux, the heating was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with a cooling ice bath (≈ 0 °C), 15 mL of aq. NH_4Cl (20%). The organic layer was separated, and the aqueous layer was extracted with dry ether (3 x 50 mL). The combined extracts were dried (K_2CO_3) overnight. The extracts were mixed with decolorized charcoal (Norit A) and filtered through a pad of celite. Evaporation of the solvent gave a yellow oil as a crude product (1.575 g, 199%). Upon adding ethyl acetate:hexanes (1:2), a white precipitate formed. The white precipitate was separated and dried (Abderhalden) (60-68 °C) overnight. Recrystallization [denatured alcohol 3A] of the precipitate yielded white flakes of **27c** (0.31 g, 39%), mp 163.5-164 °C. IR (film) 3378 (O-H), 1109 (C-O) cm^{-1}. ^{1}H NMR ($DCCl_3$) δ 1.30 [s, 3 H, CH_3]; 2.52

[s, 2 H, $H_{(1,5)}$]; 2.88-2.90 [m, 2 H, $H_{(6,8)a}$]; 3.32-3.36 [m, 2 H, $H_{(6,8)e}$]; 3.63 [S, 2 H, N-CH_2]; 3.81-3.84 [m, 2 H, $H_{(2,4)a}$]; 3.87-3.89 [m, 2 H, $H_{(2,4)e}$]; 6.42 [s, 1 H, OH]; 7.21-7.25 [t, 1 H, $H_{(4')}$]; 7.30-7.34 [t, 2 H, $H_{(3',5')}$]; 7.36-7.39 [d, 2 H, $H_{(2',6')}$]; 7.42-7.44 [d, 2 H, $H_{(2'',6'')}$]; 7.47-7.49 [d, 2 H, $H_{(3'',5'')}$]. ^{13}C NMR ($DCCl_3$) ppm 29.97 [CH_3]; 32.98 [$C(CH_3)_3$]; 37.37 [$C_{(6,8)}$]; 52.43 [$C_{(1,5)}$]; 61.23 [N-CH_2]; 68.19 [$C_{(2,4)}$]; 68.62 [$C_{(9)}$]; 124.14 [$C_{(4'')}$]; 124.49 [$C_{(1'')}$]; 125.45 [$C_{(1')}$]; 126.95 [$C_{(2',6')}$]; 127.40 [$C_{(2'',6'')}$]; 138.20 [$C_{(3',5')}$]; 139.51 [$C_{(4')}$]; 147.79 [$C_{(3'',5'')}$]. *Anal.* Calcd for $C_{24}H_{31}NO_2$: C, 78.86; H, 8.55. Found: C, 78.70; H, 8.64. Thin layer chromatography of the remaining oil showed 6 components in which the two largest and most intense components (first and last spot on TLC) were scrapped off and dissolved in $DCCl_3$. ^1H NMR analysis of first the component showed many signals in the aliphatic region (δ 1.2-4.5). This suggests that no other isomer of **27c** remained in the mixture. On the other hand, the ^1H NMR spectrum of the last component on TLC showed many signals in the aliphatic region as well. Moreover, FT-IR analysis of the last component shows a carbonyl signal (1723 cm^{-1}) from a small amount of starting material. This may indicate that the conversion was not completed even after the reaction had undergone boiling for 60 h.

7-Benzyl-9-*p*-tolyl-3-oxa-7-azabicyclo[3.3.1]nonan-9-ol (27d). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 3.24 mL (0.0065 mol, 2 *M*) of *p*-tolylmagnesium bromide in diethyl ether, and the contents were stirred at RT under N_2 for 5 min. A solution of ketone **21a** (0.5 g, 0.0022 mol) in anhydrous THF (5 mL) was added dropwise to the Grignard reagent in the flask over 0.5 min. Upon applying heat for 1 h, the light yellow mixture turned to brown and

then to a clear orange liquid. After 60 h at reflux, the heat was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with a cooling ice bath (≈ 0 °C), 15 mL of aq. NH_4Cl (20%). The organic layer was separated, and the aqueous layer was extracted with dry ether (3 x 50 mL). The combined extracts were dried (K_2CO_3) overnight. The extracts were mixed with decolorized charcoal (Norit A) and filtered through a pad of celite. Evaporation of the solvent gave a yellow oil as a crude product (0.827 g, 116%). The FT-IR analysis showed 2 strong signals for OH peak at 3334 cm^{-1} and C=O peak of starting ketone at **21a** at 1710 cm^{-1}. Thin layer chromatography of crude oil showed many signals in the aliphatic region as well as in aromatic region. This suggests many side reactions occurred after the mixture was subjected to 60 h of reflux.

7-Benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (28). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 24 mL (0.012 mol, 0.5 *M*) of 4-*N,N*-dimethylamino-phenylmagnesium bromide in THF, and the contents were stirred at RT under N_2 for 5 min. The solution of ketone **21b** (0.5 g, 0.002 mol) in anhydrous THF (10 mL) was added dropwise (0.5 h) to the Grignard reagent. Upon applying heat (≈ 1 h), the light yellow mixture turned copper color. After heating for 24 h at gentle reflux, the heat was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with a cooling ice bath (≈ 0 °C), 60 mL of aq. NH_4Cl (10%) and 5 mL of H_2SO_4 (18 *M*) with stirring. After 1 h, the mixture was made basic (cooling ice bath) *via* addition of KOH pellets (pH ≈12). The mixture was extracted with dry ether (3 x 50

mL), and the combined extracts were dried (KOH) overnight. The mixture was decolorized with charcoal (Norit A) and filtered through a celite pad. Evaporation of the solvent gave a brown oil as the crude product. The oil was purified via flash column chromatography with ethyl acetate:hexanes [1:8] and methanol:CH_2Cl_2 [1:35]. Evaporation of the solvent (methanol:CH_2Cl_2), gave an oil, which upon standing at RT, yielded a dark brown solid. The product was recrystallized [denatured alcohol 3A:ether, 4:1], to yield the final product as colorless crystals of **28** (0.33 g, 44%), mp 168-169.5 °C. IR (film) 3276 (O-H) cm^{-1}. ^1H NMR ($DCCl_3$) δ 2.22-2.26 [d, 2 H, $H_{(6,8)a}$]; 2.65-2.69 [dd, 2 H, $H_{(6,8)e}$]; 2.89 [s, 2 H, $H_{(1,5)}$]; 2.95 [s, 6 H, $N(CH_3)_2$]; 3.34-3.37 [d, 2 H, $H_{(2,4)e}$]; 3.42 [s, 2 H, CH_2]; 3.48-3.52 [dd, 2 H, $H_{(2,4)a}$]; 4.75 [s, 1 H, OH]; 6.68-7.30 [m, 4 H, Ar-*H*];. ^{13}C NMR ($DCCl_3$) ppm 40.24 [$C_{(2,4)}$]; 53.77 [$C_{(1,5)}$]; 54.94 [$C_{(6,8)}$]; 61.92 [CH_2]; 69.40 [$C_{(9)}$]; 112.28 [$C_{(3'',5'')}$]; 126.64 [$C_{(4')}$]; 127.17 [$C_{(3',5')}$]; 128.36 [$C_{(2',6')}$]; 129.04 [$C_{(2'',6'')}$]; 129.68 [$C_{(1'')}$]; 137.76 [$C_{(1')}$]; 149.84 [$C_{(4'')}$]. *Anal.* Calcd for $C_{22}H_{28}N_2OS$: C, 71.70; H, 7.66. Found: C, 71.80; H, 7.66.

7-Benzyl-9-(4-*t*-butylphenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (29). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 3.03 mL (0.006 mol, 2 *M*) of 4-*tert*-butylphenylmagnesium bromide in diethyl ether, and the contents were stirred at RT under N_2 for 5 min. A solution of ketone **21b** (0.5 g, 0.002 mol) in anhydrous THF (5 mL) was added dropwise to the Grignard reagent in the flask over 0.5 min. Upon applying heat for 1 h, the light yellow mixture turned to brown and then to a clear orange liquid. After 60 h at reflux, heating was discontinued, but stirring was maintained overnight at RT. To the mixture was

added dropwise, with a cooling ice bath (≈ 0 °C), 15 mL of aq. NH_4Cl (20%). The organic layer was separated, and the aqueous layer was extracted with dry ether (3 x 50 mL). The combined extracts were dried (K_2CO_3) overnight. The extracts were mixed with decolorized charcoal (Norit A) and filtered through a pad of celite. Evaporation of the solvent gave a yellow oil as the crude product (0.97 g, 127%). The IR spectrum of the reaction mixture showed an OH peak at 3337 cm^{-1} and small ketone peak of starting ketone at **21b** at 1707 cm^{-1}. It was not possible to isolate **29**.

7-Benzyl-9-*p*-tolyl-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (30). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, an addition funnel, a condenser with a N_2 inlet and a glass stopper. The flask was charged with 3.03 mL (0.006 mol, 2 *M*) of *p*-tolylmagnesium bromide in diethyl ether, and the contents were stirred at RT under N_2 for 5 min. A solution of ketone **21b** (0.5 g, 0.002 mol) in anhydrous THF (5 mL) was added dropwise to the Grignard reagent in the flask over 0.5 min. Upon applying heat for 1 h, the light yellow mixture turned to brown and then to a clear orange liquid. After 60 h at reflux, heating was discontinued, but stirring was maintained overnight at RT. To the new mixture was added dropwise, with a cooling ice bath (≈ 0 °C), 15 mL of aq. NH_4Cl (20%). The organic layer was separated, and the aqueous layer was extracted with dry ether (3 x 50 mL). The combined extracts were dried (K_2CO_3) overnight. The extracts were mixed with decolorized charcoal (Norit A) and filtered through a pad of celite. Evaporation of the solvent gave a yellow oil as the crude product (0.88 g, 135%). The FT-IR analysis showed 2 strong signals for OH peak at 3342 cm^{-1} and C=O peak of starting ketone at **21a** at 1711 cm^{-1}. Thin layer chromatography of crude oil showed many signals in the aliphatic region as well as in

aromatic region. This suggests many side reactions occurred after the mixture was subjected to 60 h of reflux. It has not been possible to isolate **30**.

Part C: The Procedures of Single Crystal X-ray Diffraction Analyses

4-(3,5-Dimethylphenyl)tetrahydrothiopyran-4-ol (26j).[69] A single crystal [orthorhombic, Pna2(1)] of **26j** was mounted on Bruker-Siemans-Nicolet P4 diffractometer equipped with a molybdenum source (graphite monochromator, MoKα radiation, 1 = 0.71703 Å) and a θ-2θ data collection [variable scan rate between 10 and 30 seconds per degree, based upon the intensity observed per scan] (Table VII). The unit cell was determined by least squares refinement of the best angular positions for 48 independent reflections. Data (1955 points) were collected at 301 K (Table VII) and corrected for Lorentz, polarization, and background effects. The intensities of three standard reflections were monitored after every 97 reflections. Crystal decomposition was found to be significant. After removal of redundant and space group forbidden data, atomic positions were determined with SHELXS, and 1150 observed data (I>3.0_(I)) were refined using full matrix least squares [function minimized, $\Sigma w(Fo^2-Fc^2)^2$] until convergence (SHELXL). Hydrogen positions were calculated and included in the final cycles of refinement in constrained positions and with fixed isotopic thermal parameters and with C-H distance of 0.97 Å. Absorption corrections were made using a semi-empirical method based on psi-scans. Extinction was defined but was minimal. Molecular graphics were prepared using the program, XP. The final cycle of refinement led to an agreement factors of R = 5.39% and Rw = 9.15% with 137 parameters refined.

7-Benzyl-9-(4-*N,N*-dimethylaminophenyl)-3-thia-7-azabicyclo[3.3.1]nonan-9-ol (28). The data were collected at 100(2) K on a Bruker Apex diffractometer[58,60] using MoKα (λ = 0.71073 Å) radiation. Intensity data, which approximately covered the full sphere of the reciprocal space, were measured as a series of ω oscillation frames each 0.3 for 25 sec/ frame. The detector was operated in the 512 x 512 mode and was positioned 6.12 cm from the crystal. Coverage of unique data was 99.7% complete to 55.0 (2θ). Cell parameters were determined from non-linear least squares fit of 4123 reflections in the range of $3.2 < \theta < 26.9$. A total of 16383 reflections were measured.

The structure was solved by the direct method using SHELXTL system,[59] and refined by full-matrix least squares on F^2 using all reflections. All the non-hydrogen atoms were refined anisotropically. All the hydrogen atoms were included with idealized parameters. Final R1 = 0.027 is based on 4222 "observed reflections" [$I > 2\sigma(I)$], and wR2 = 0.071 is based on all reflections (4293 reflections). Thermal ellipsoids were drawn at 50% level.

Part D: The preparation of derivatives of tertiary alcohols.

Commercial (Aldrich) 4-dimethylaminopyridine (DMAP), triethylamine (TEA), and acetic anhydride were used directly. Glassware was oven-dried overnight before use. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR unit. NMR spectra were recorded on a Varian Gemini 2000 HR spectrometer (400 MHz) operating at 399.90 MHz (^1H) and 100.56 MHz (^{13}C). Mps were taken on a Thomas-Hoover apparatus and were uncorrected. The single apostrophe on a carbon is for carbon in the aromatic ring.

Acetic Acid 4-(3,5-Dimethylphenyl)tetrahydrothiopyran-4-yl Ester (26j'): In a 15-mL, 3-necked, round-bottom flask equipped with a condenser, a magnetic stirring bar, and a N_2 inlet was added alcohol **26j** (0.5 g, 2.25 mmol), acetic anhydride (0.53 g, 4.50 mmol), and triethylamine (TEA, 0.45 g, 4.50 mmol). To a stirring mixture was added in one portion 4 mol% of dimethylaminopyridine (DMAP, 0.011 g, 0.09 mmol). The

reaction mixture was heated for 12 h at 80 °C. The reaction mixture was then taken up in 15 mL of *n*-hexane, and the solution was washed with HCl solution (5%, 15 mL), saturated $NaHCO_3$ (15 mL) and brine (15 mL) and was finally dried (K_2CO_3, overnight). Evaporation of the *n*-hexane yielded yellow crystals which were washed with ice cold hexane to afford colorless crystals of **26j'** (0.45 g, 75.6%), mp 105-106 °C. IR 1738 (C=O), 1194 (C-O) cm^{-1}. ^1H NMR ($DCCl_3$) δ 2.02-2.12 [m, 2 H, $H_{(3,5)a}$], 2.11 [s, 3 H, C(O)CH_3], 2.30 [s, 3 H, Ar-CH_3], 2.48-2.54 [m, 2 H, $H_{(3,5)e}$], 2.75-2.80 [m, 2 H, $H_{(2,6)a}$], 3.01-3.10 [m, 2 H, $H_{(2,6)e}$], 6.89 [s, 2 H, Ar-$H_{(othor)}$], 7.25 [s, 1 H, Ar-$H_{(para)}$]; ^{13}C NMR ($DCCl_3$) ppm 21.56 [C(O)-CH_3], 22.08 [Ar-CH_3], 24.05 [$C_{(3,5)}$], 37.44 [$C_{(2,6)}$], 80.93 [$C_{(4)}$], 121.90 [$C_{(2',6')}$], 129.06 [$C_{(4')}$], 137.86 [$C_{(3',5')}$], 145.13 [$C_{(1')}$],169.30 [*C*=O]. *Anal.* Calcd for $C_{15}H_{20}O_2S$: C, 68.14; H, 7.62. Found: C, 68.10; H, 7.71.

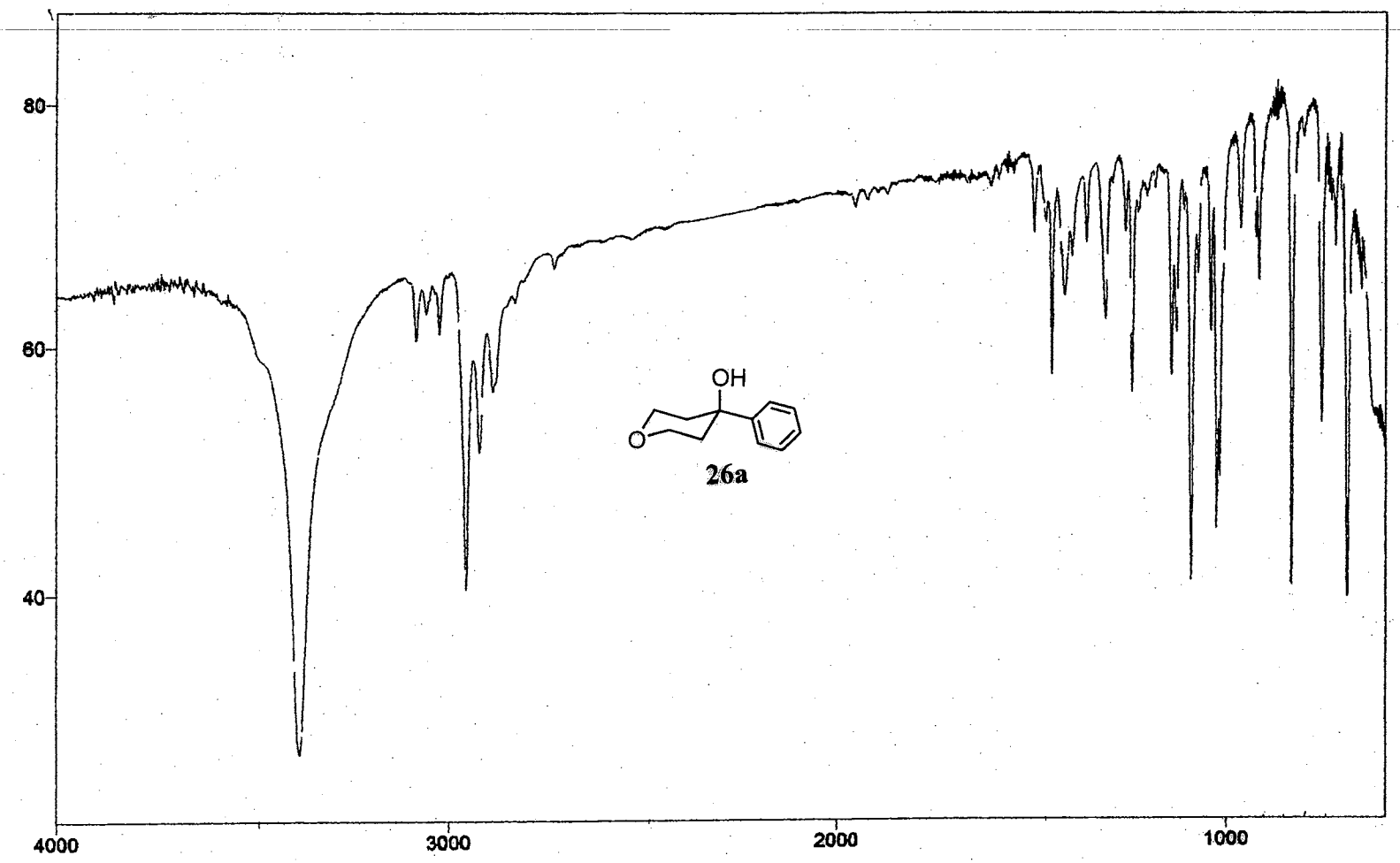
Attempted Synthesis of Acetic acid 7-Benzyl-9-(4-*N*,*N*-dimethylaminophenyl)-3-oxa-7-azabicyclo[3.3.1]nonan-9-yl Ester (27b'): In a 15-mL, 3-necked, round-bottom flask equipped with a condenser, a magnetic stirring bar, and a N_2 inlet was added alcohol **27b** (0.1 g, 0.28 mmol), acetic anhydride (0.067 g, 0.56 mmol), and triethylamine (TEA, 0.057 g, 0.56 mmol). To the stirred mixture was added in one portion 4 mol % of dimethylamino-pyridine (DMAP, 0.014 g, 0.011 mmol). The reaction mixture was heated for 12 h at 80 °C. The resulting reaction mixture was taken up in 15 mL of *n*-hexane, and the solution was washed with HCl solution (5%, 15 mL), saturated $NaHCO_3$ (15 mL) and brine (15 mL) and was then dried (K_2CO_3, overnight). Evaporation of *n*-hexane yielded colorless crystals of starting alcohol **27b**. IR (film) 3378 (O-H) cm^{-1}.

Part E: The preparation of *N,N'*-diphenylurea **51**.[18]

*Commercial (Aldrich) phenyl isocyanate (**50**) was used directly. Solvents were dried (24 h) over molecular sieves (3A). Glassware was oven-dried overnight before use. IR spectra were recorded on a Perkin-Elmer 2000 FT-IR unit. NMR spectra were recorded on a Varian Gemini 2000 HR spectrometer (300 MHz) operating at 300.09 MHz (^{1}H) and 75.46 MHz (^{13}C). Mps were taken on a Thomas-Hoover apparatus and were uncorrected.*

Procedure: In a 15-mL, 3-necked, round-bottomed flask equipped with a condenser, a magnetic stirring bar, and a N_2 inlet was placed a solution of phenyl isocyanate (**50**, 0.031 g, 0.26 mmmol) in dry benzene (2 mL) [or toluene] which was then heated under gentle reflux with stirring for 30 min. Heating was discontinued, but stirring was maintained until the flask had cooled to RT. The organic solution was washed with water (2 mL) and then brine (2 mL). After separation, the aqueous layer was extracted with dry ether (5 mL). The combined organic layer/extracts were dried (Na_2SO_4), and evaporation of solvent under vacuum gave a white solid in a good yield and high purity (Table XIII). A reaction scaled up to 1.0 g gave similar results. Performing the reaction in toluene avoids the use of benzene which had been classified as a moderate carcinogen.[3] A highly crystalline product, mp. 242-243 °C, could be obtained if the solvents were allowed to evaporate slowly at RT over 2-3 days. However, the overall yield of **51** was low for reasons not clear at this time. The sample of **51** from toluene was slightly purer than from benzene. TLC analysis with ethyl acetate:ether (1:3, 1:5, and 1:8) showed one spot for **51** obtained from runs in benzene or toluene. The IR, ^{1}H NMR and ^{13}C NMR spectra (DMSO-d_6) of **51** were identified by comparison with those reported for *N,N'*-diphenylurea.[12,17] FT-IR (KBr) 3324 (N-*H*); 1646 (C=O) cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 8.66 (s, N-*H*); 7.34-7.45 (d, 2 H, Ar-*H*); 7.24-7.29 (t, 2 H, Ar-*H*); 6.93-6.97 (t, 1 H, Ar-*H*); ^{13}C NMR (DMSO-d_6): ppm 152.55 (C=O); Ar-*C*: 139.74, 128.77, 121.76, 118.14.

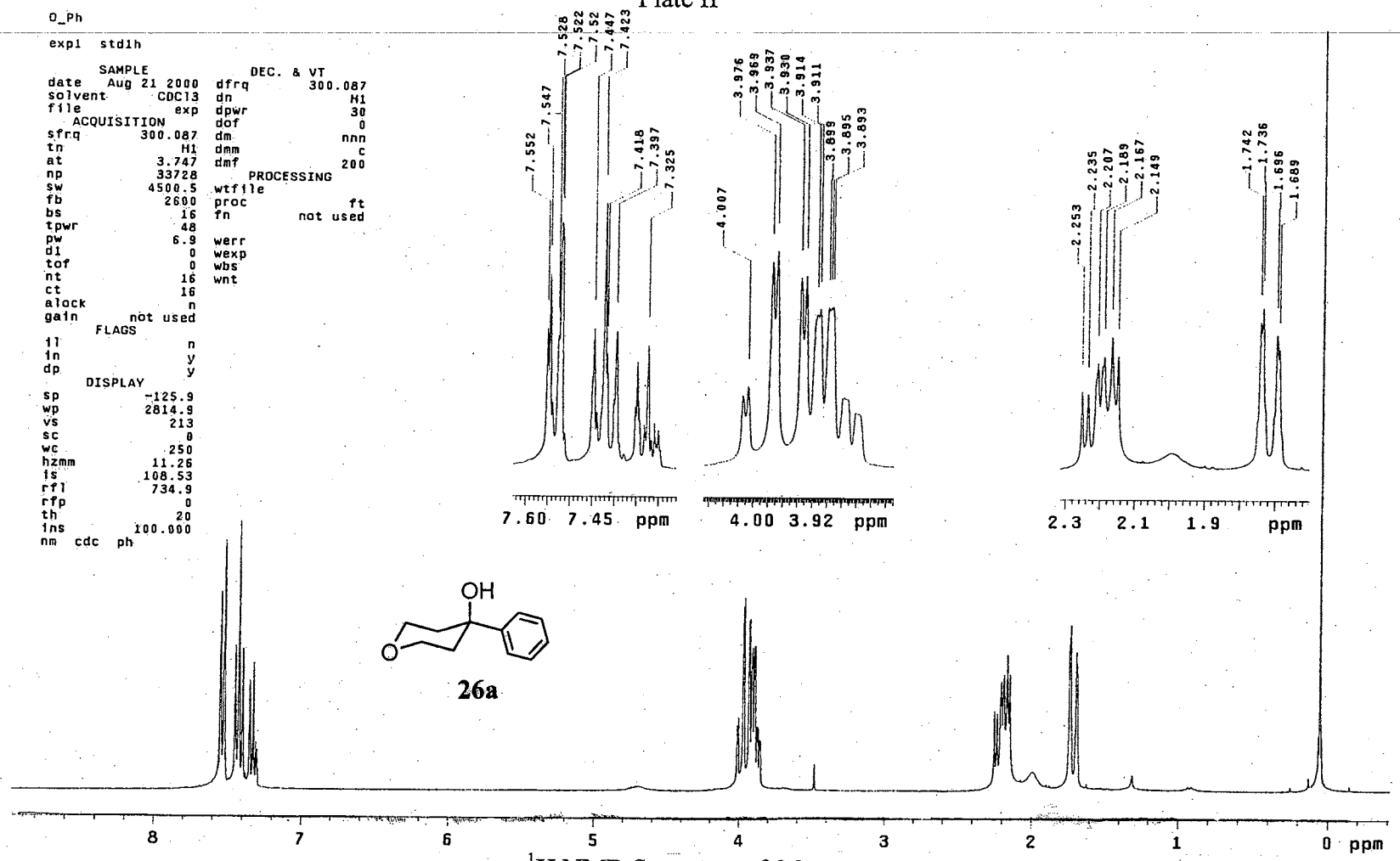
Plate I



26a

IR Spectrum of **26a**

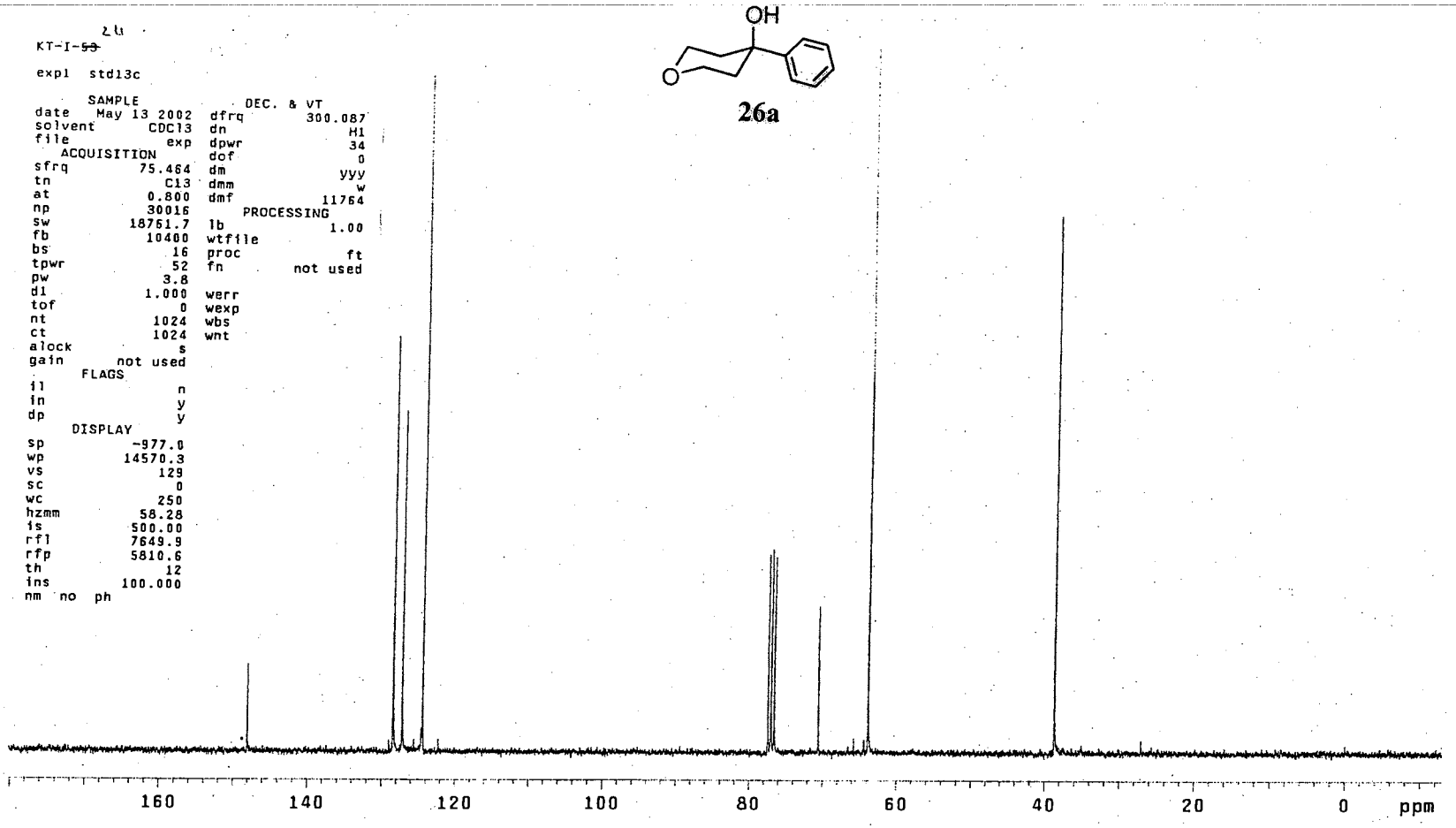
Plate II



26a

^{1}H NMR Spectrum of **26a**

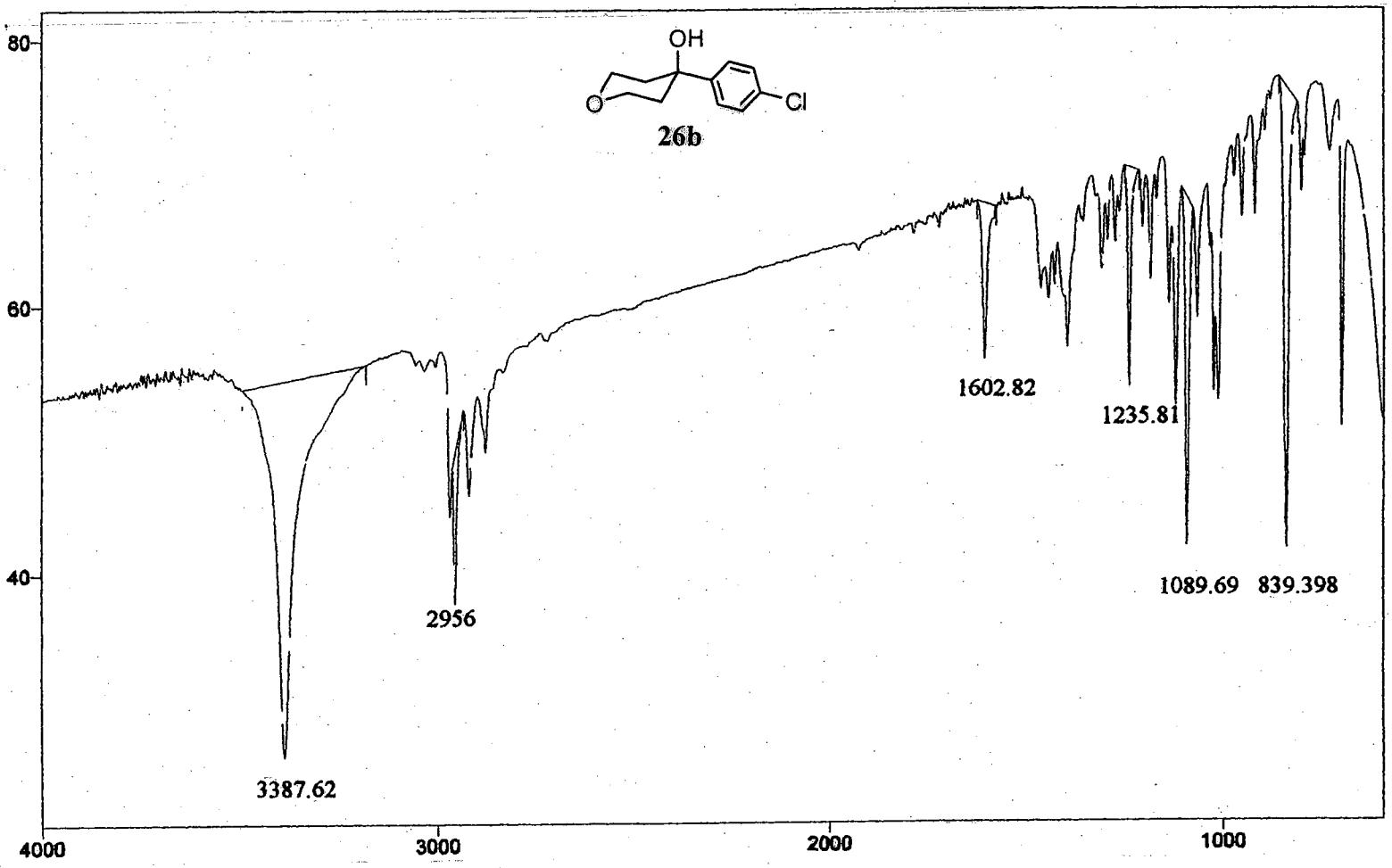
Plate III



26a

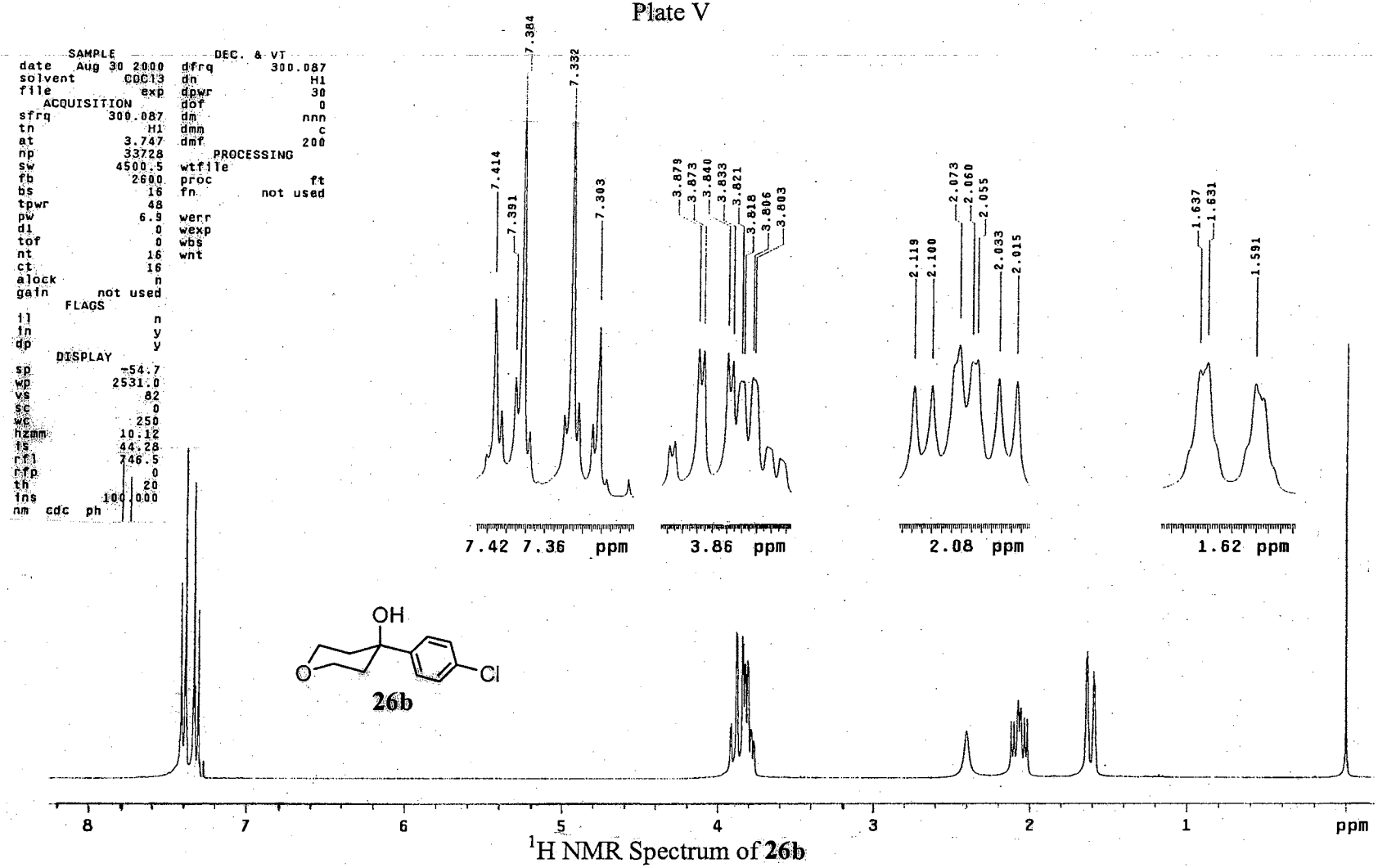
^{13}C NMR Spectrum of **26a**

Plate IV



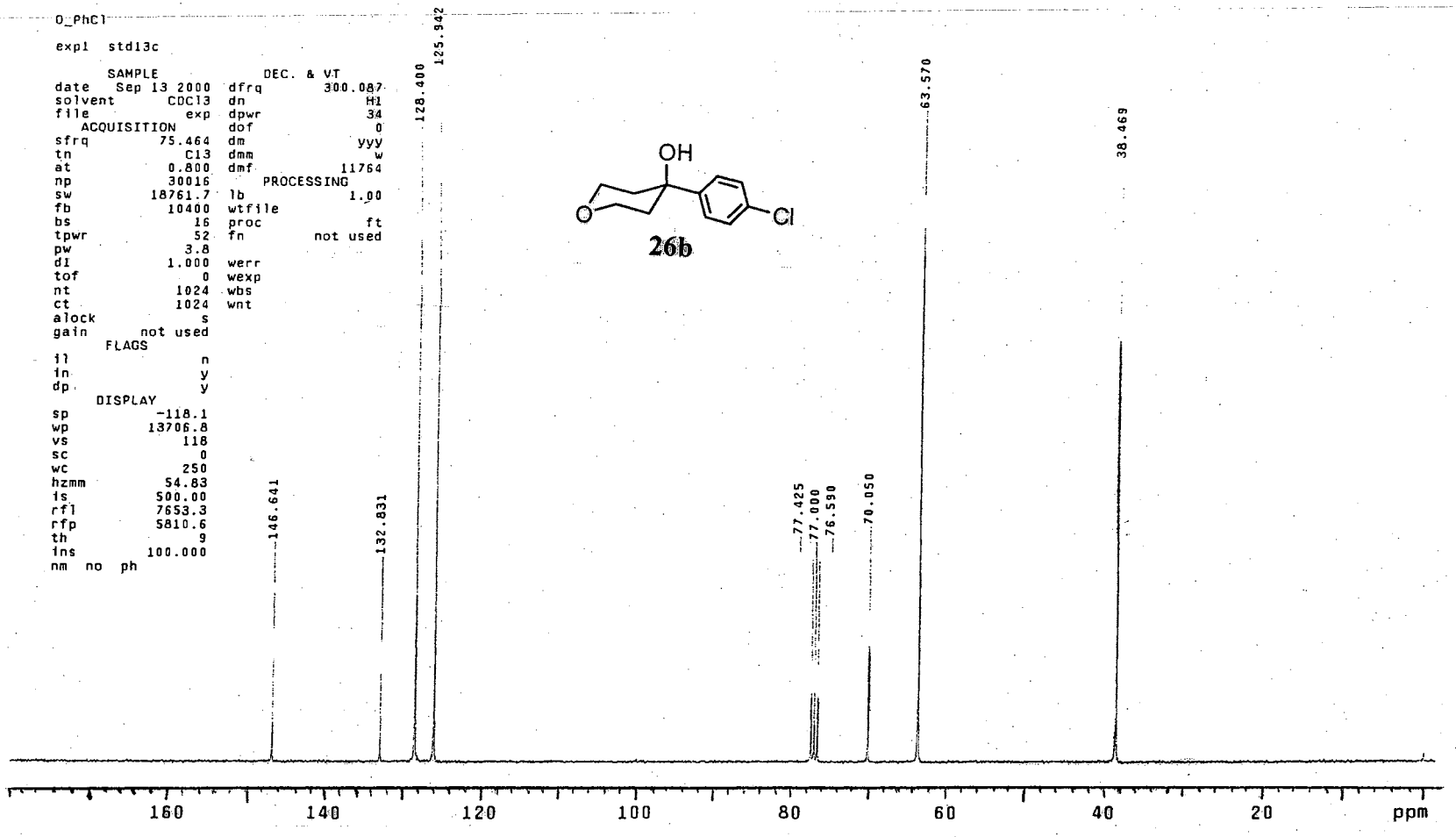
IR Spectrum of **26b**

Plate V



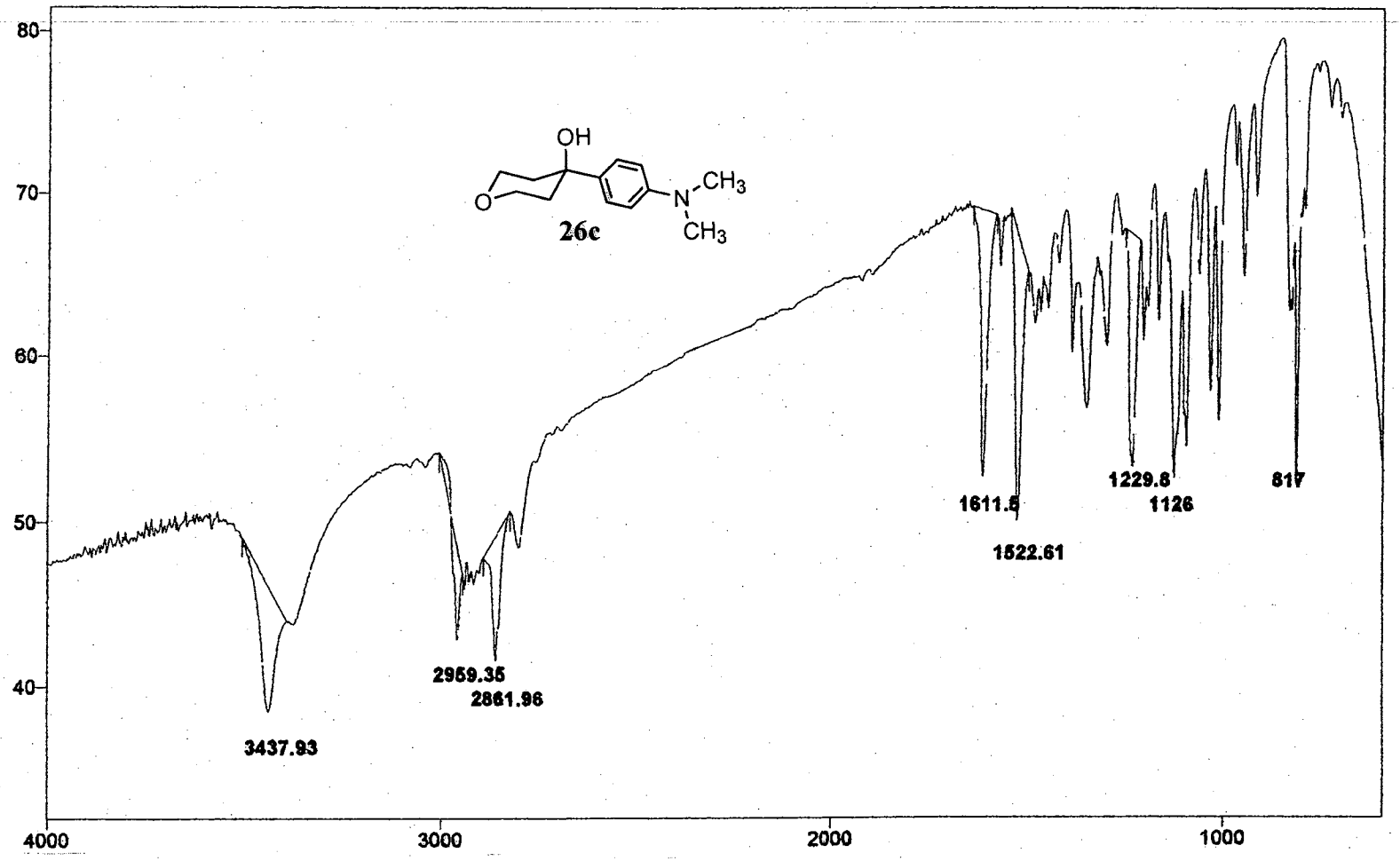
^{1}H NMR Spectrum of **26b**

Plate VI



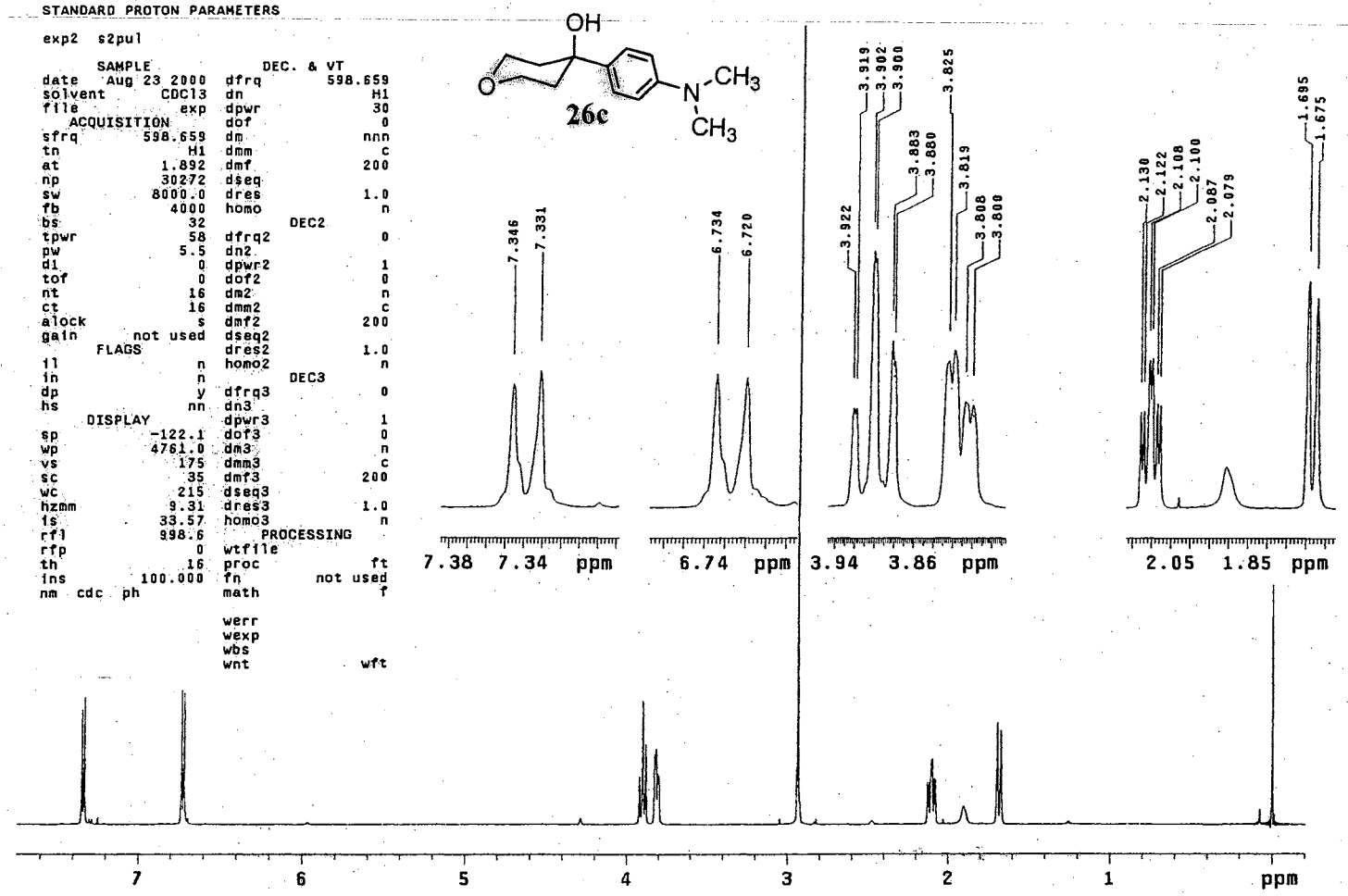
^{13}C NMR Spectrum of **26b**

Plate VII



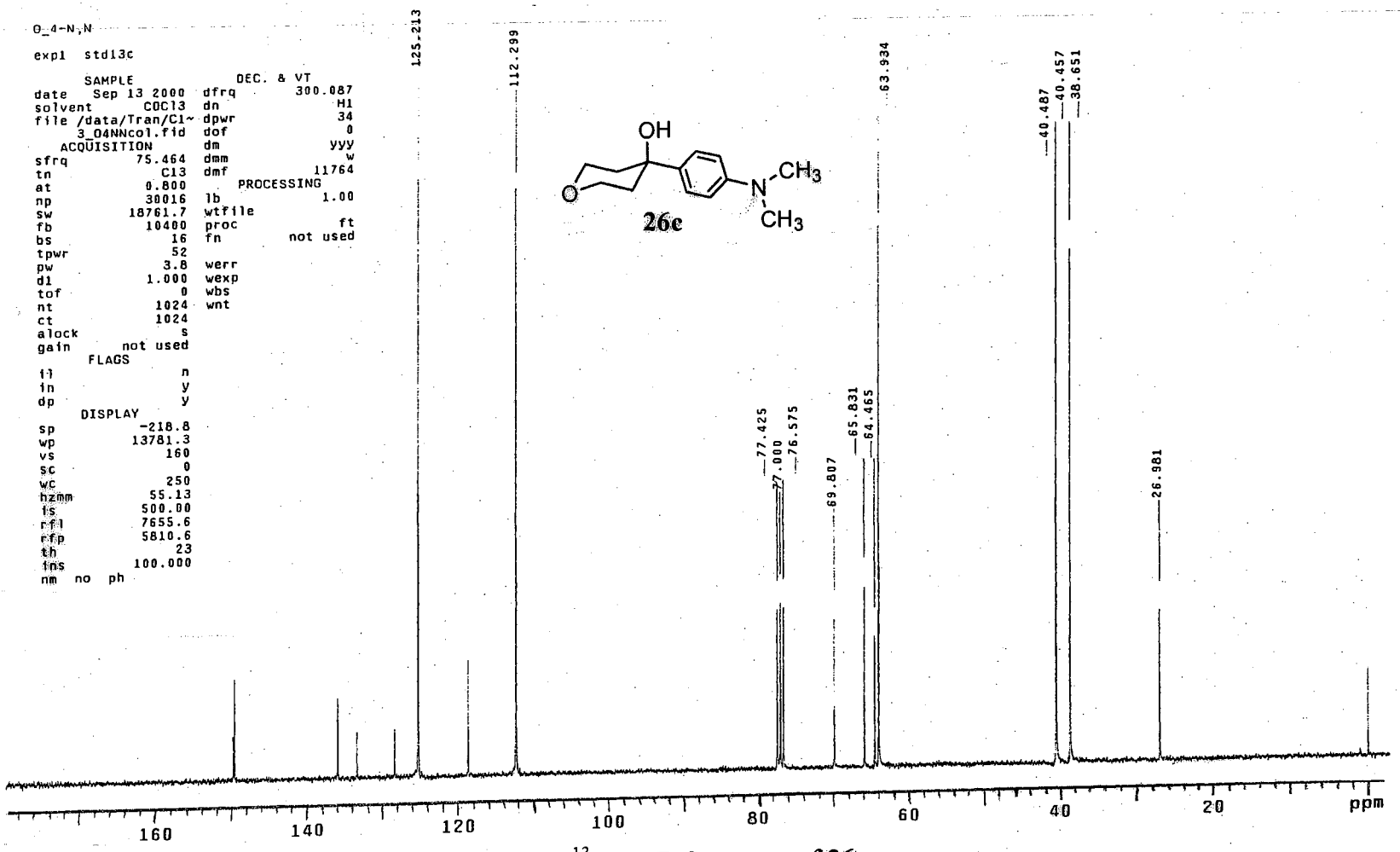
IR Spectrum of **26c**

Plate VIII



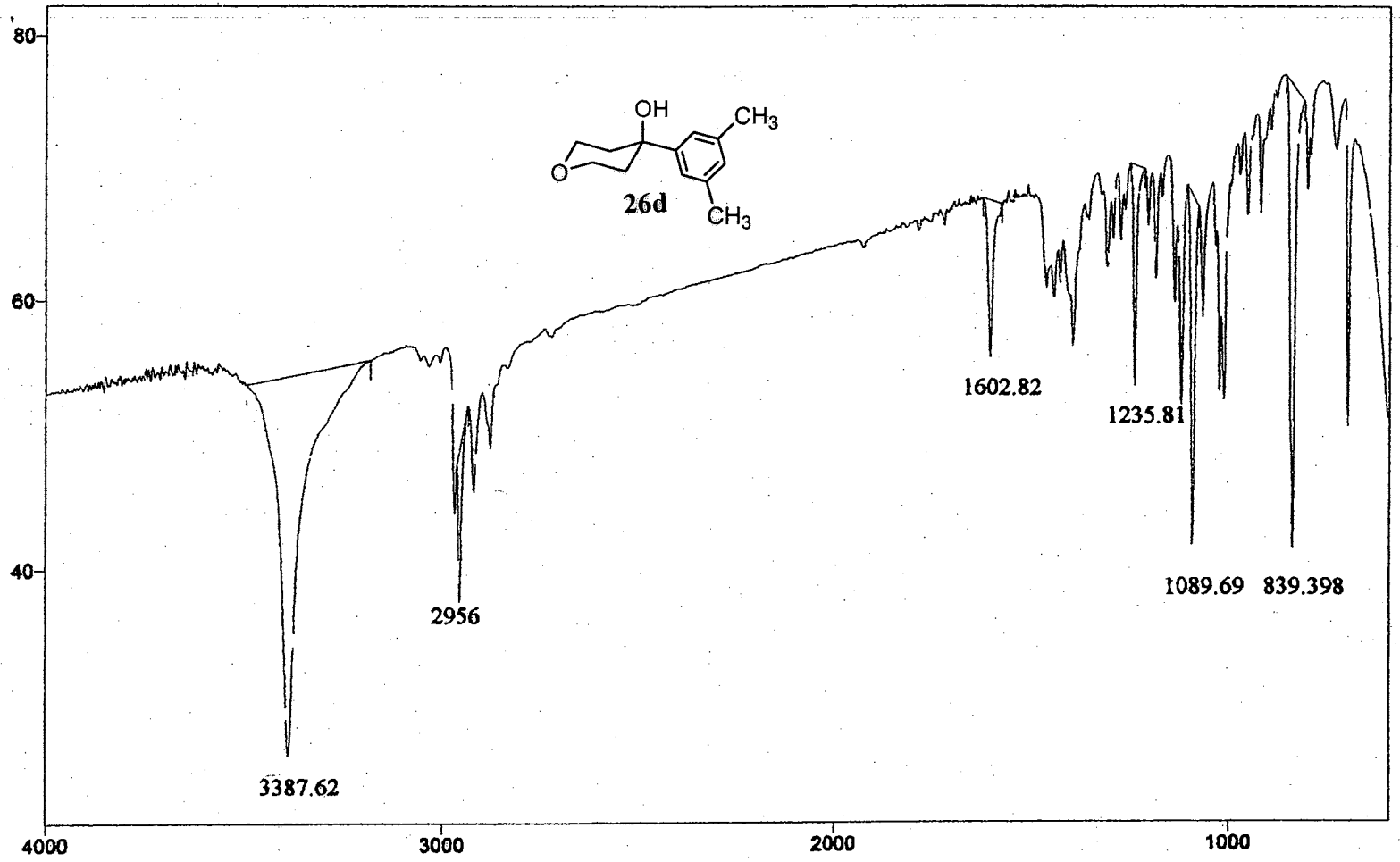
^{1}H NMR Spectrum of **26c**

Plate IX



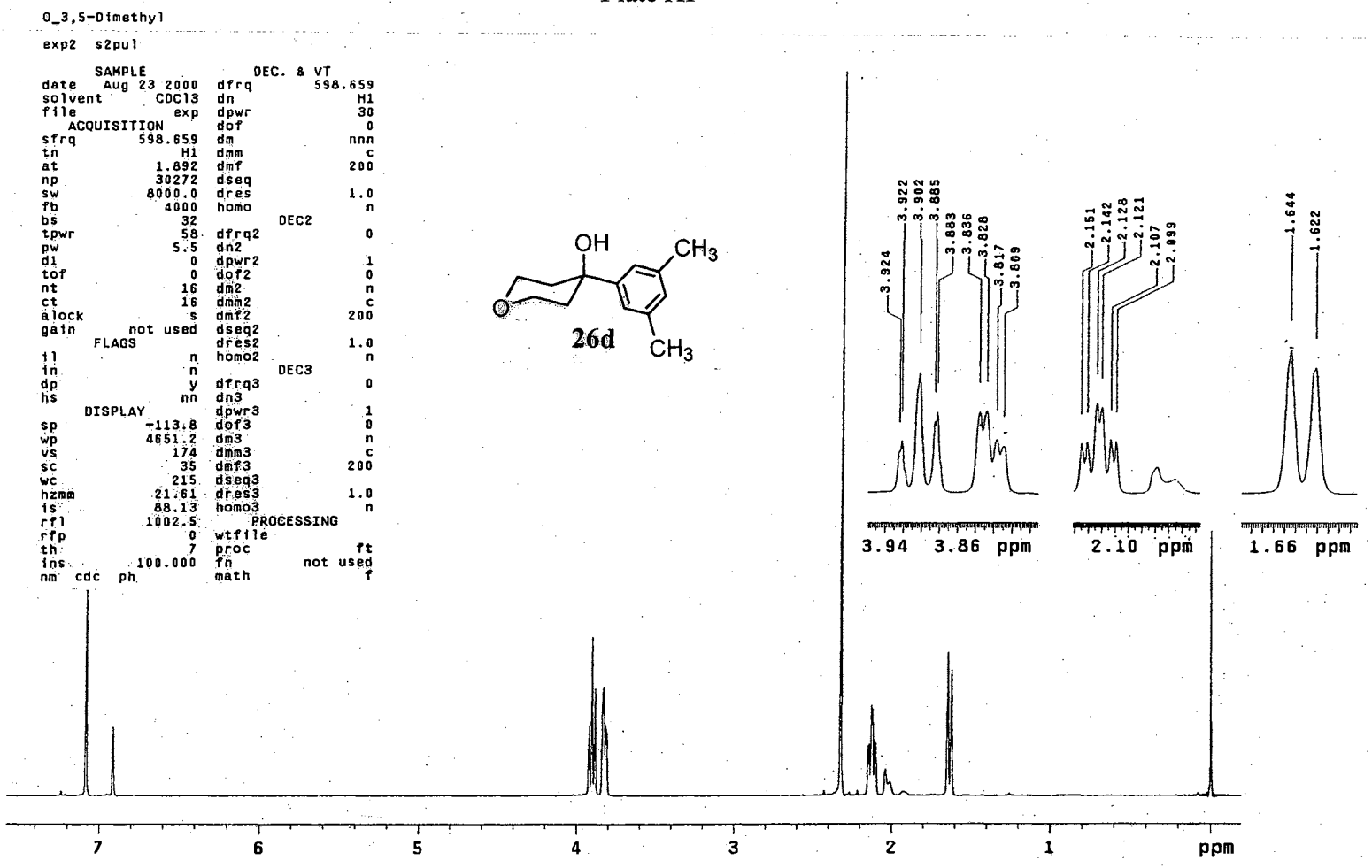
^{13}C NMR Spectrum of **26c**

Plate X



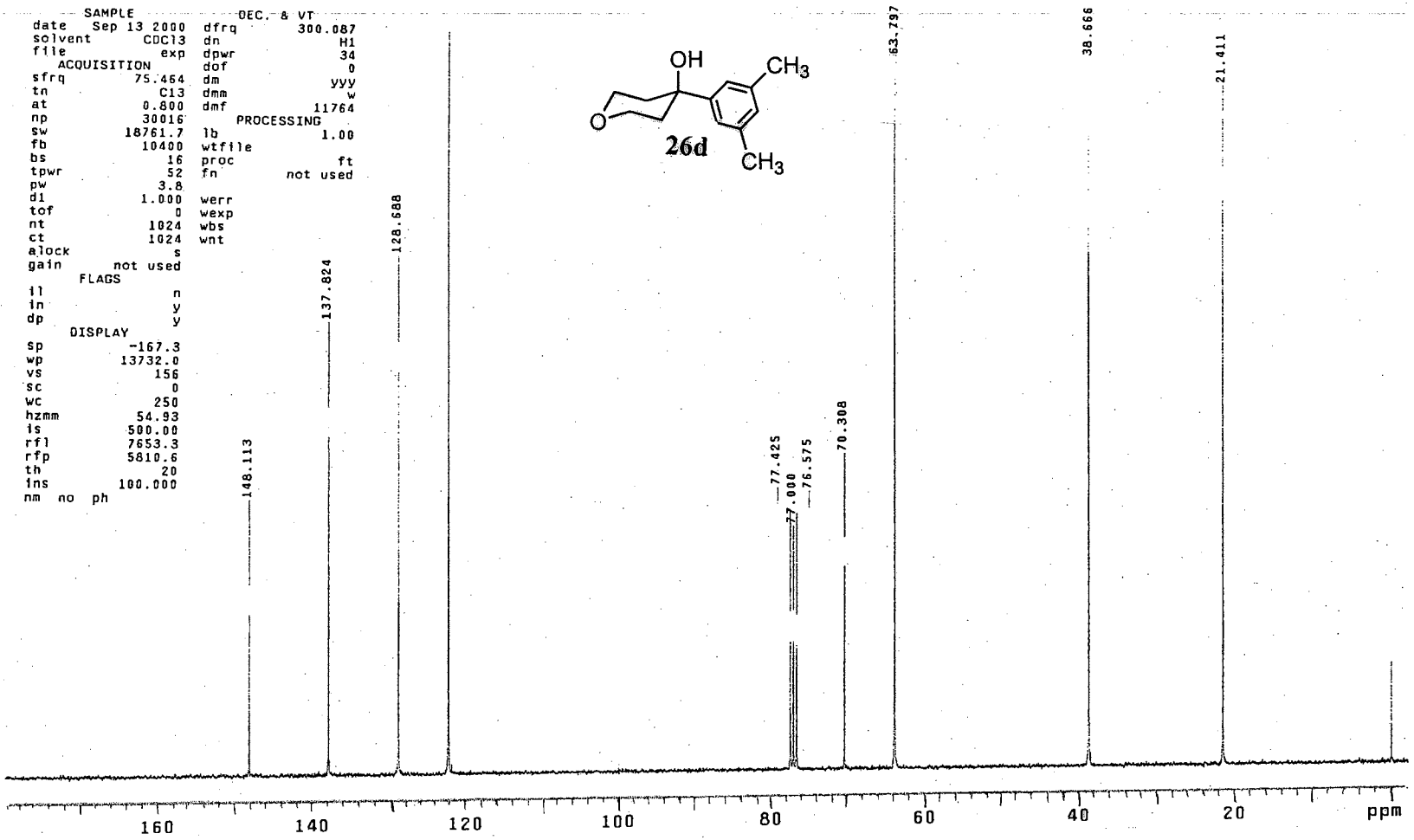
IR Spectrum of **26d**

Plate XI



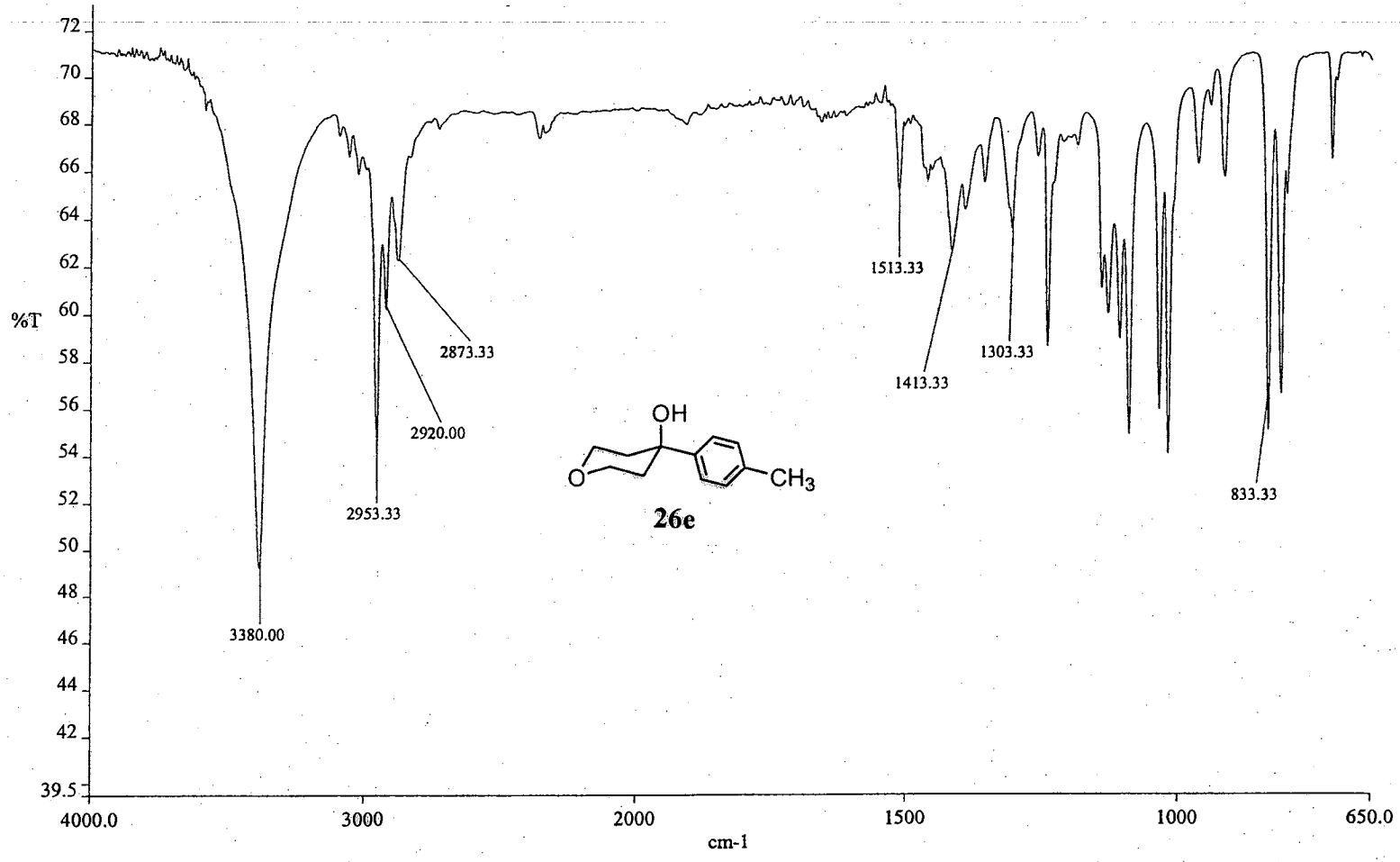
^{1}H NMR Spectrum of **26d**

Plate XII



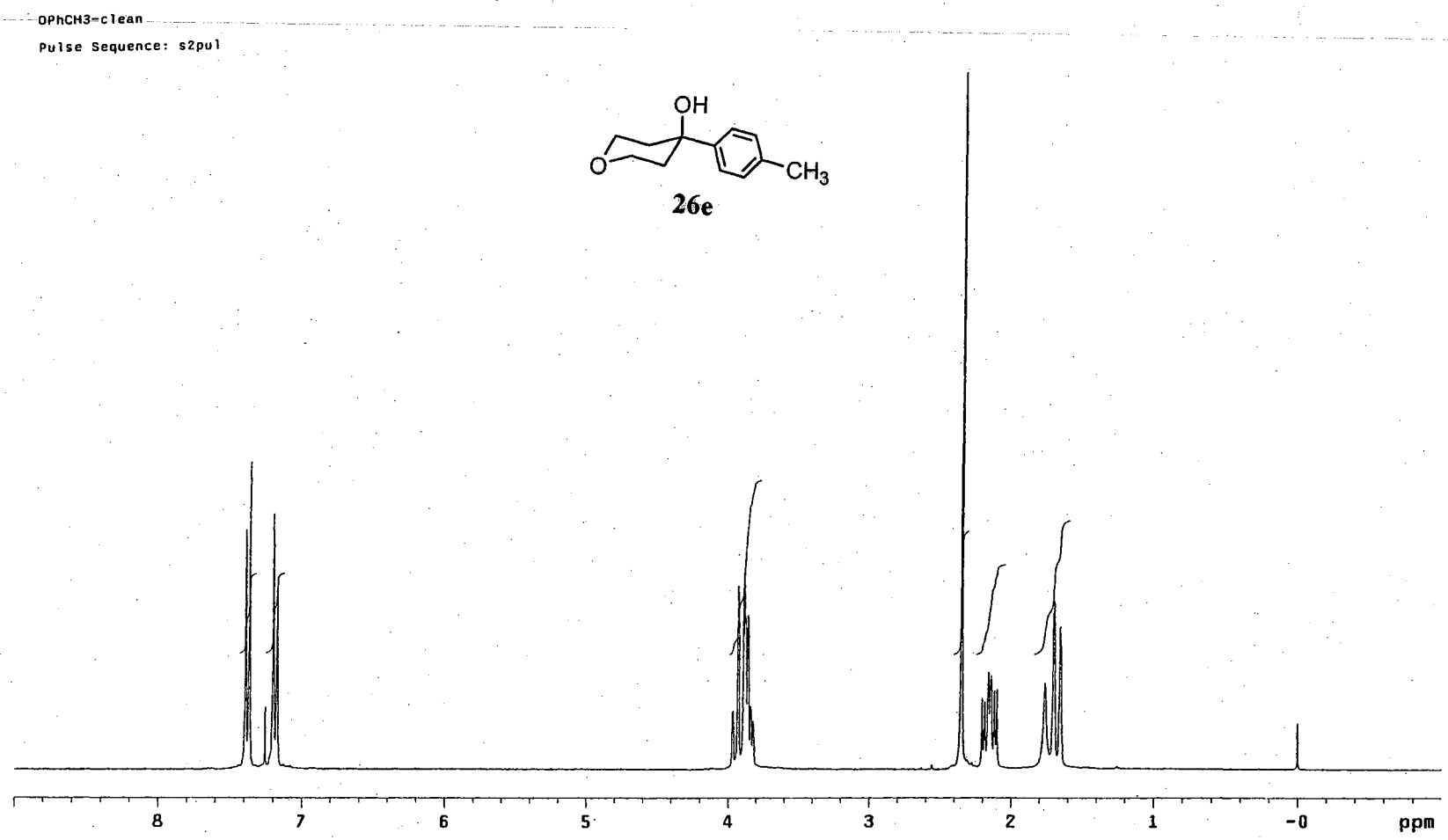
^{13}C NMR Spectrum of **26d**

Plate XIII



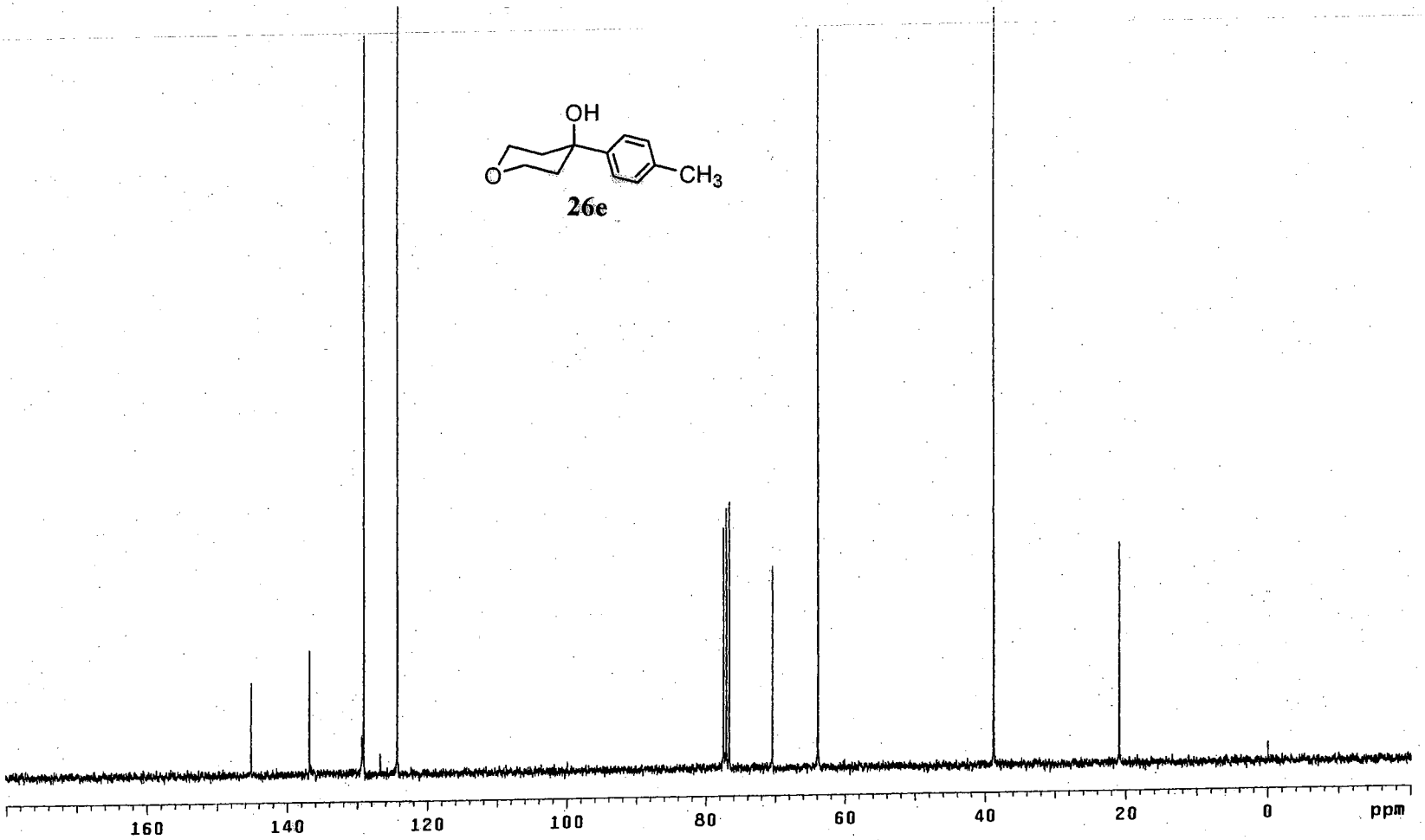
IR Spectrum of **26e**

Plate XIV



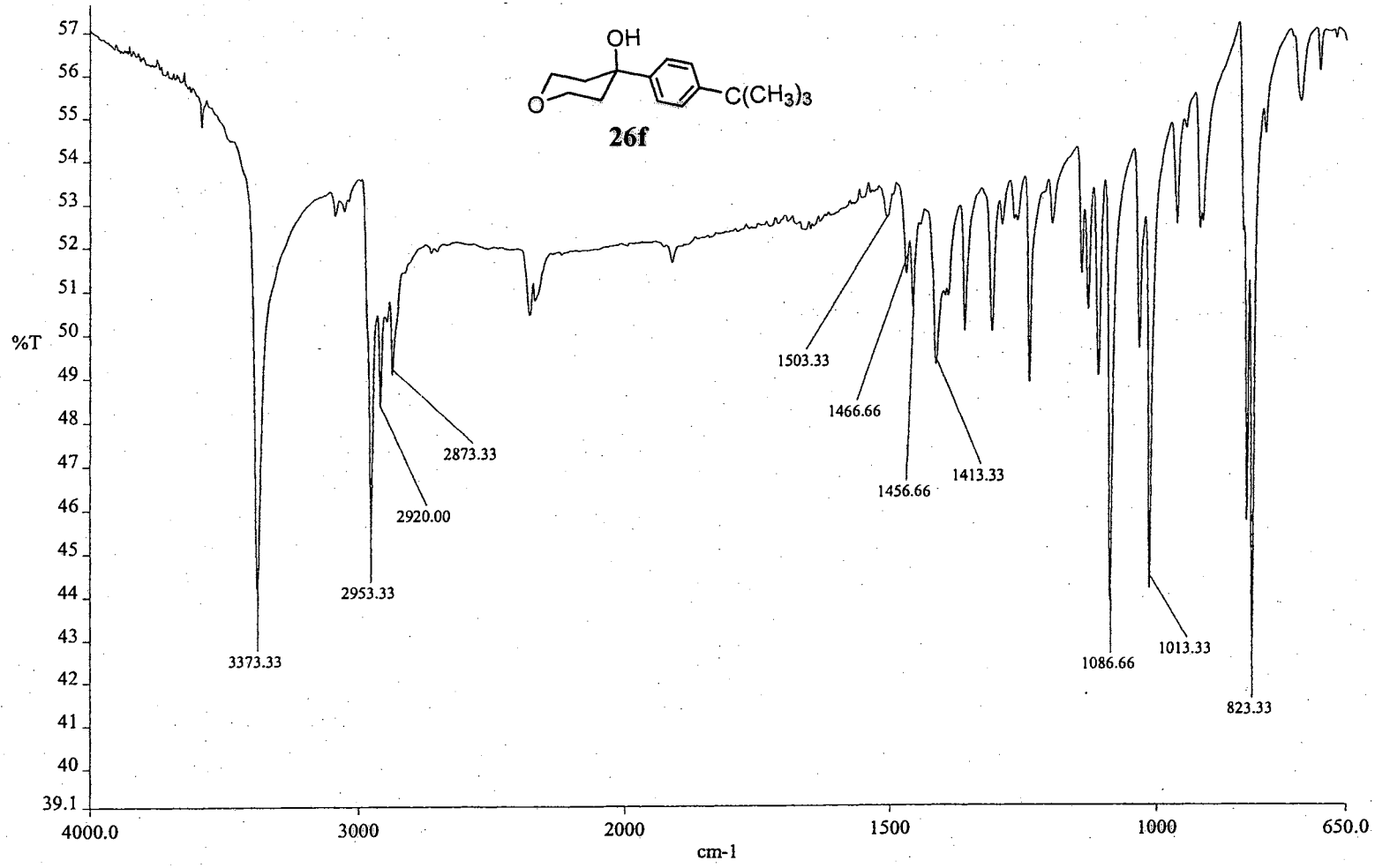
^{1}H NMR Spectrum of **26e**

Plate XV



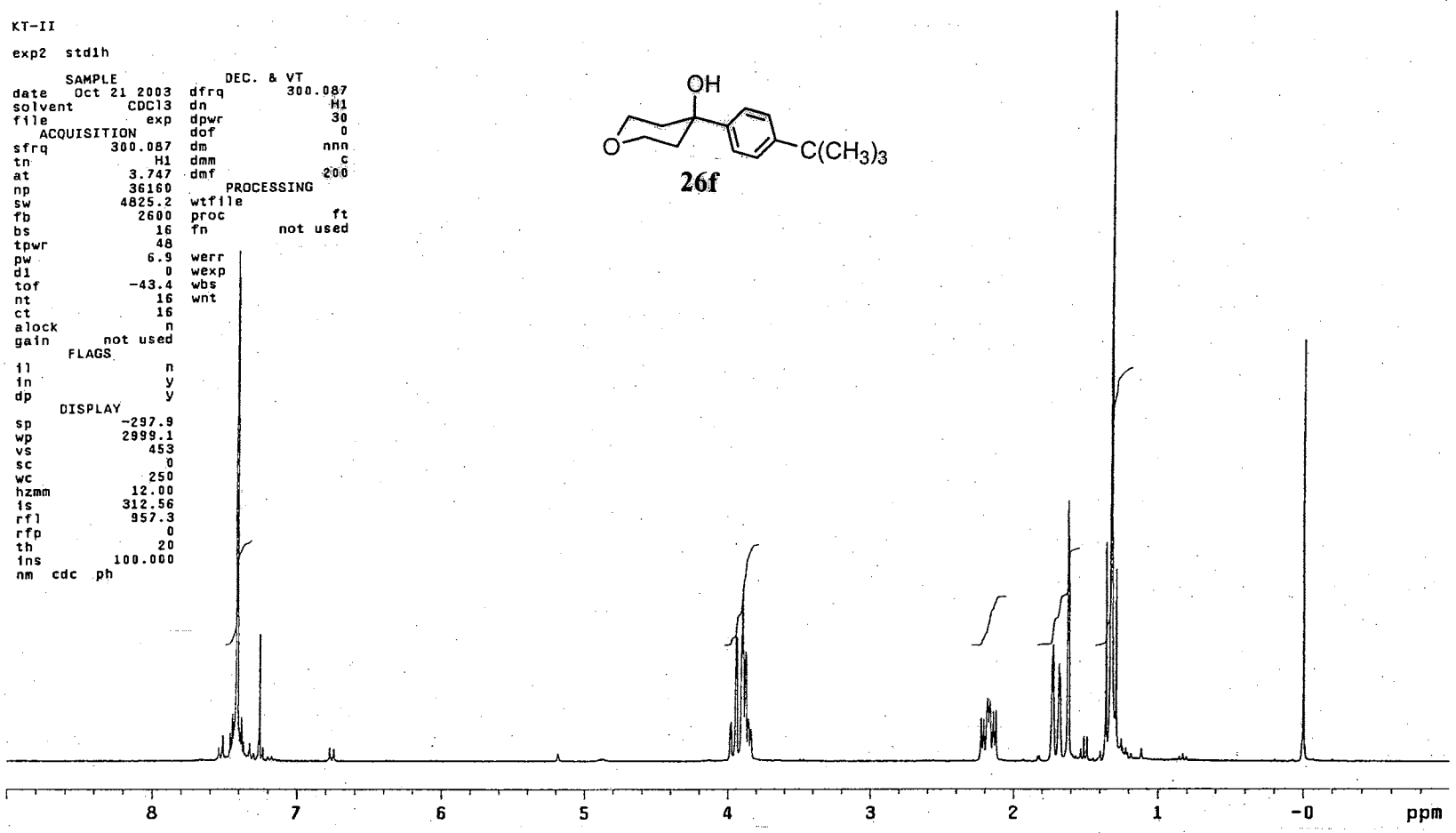
^{13}C NMR Spectrum of **26e**

Plate XVI



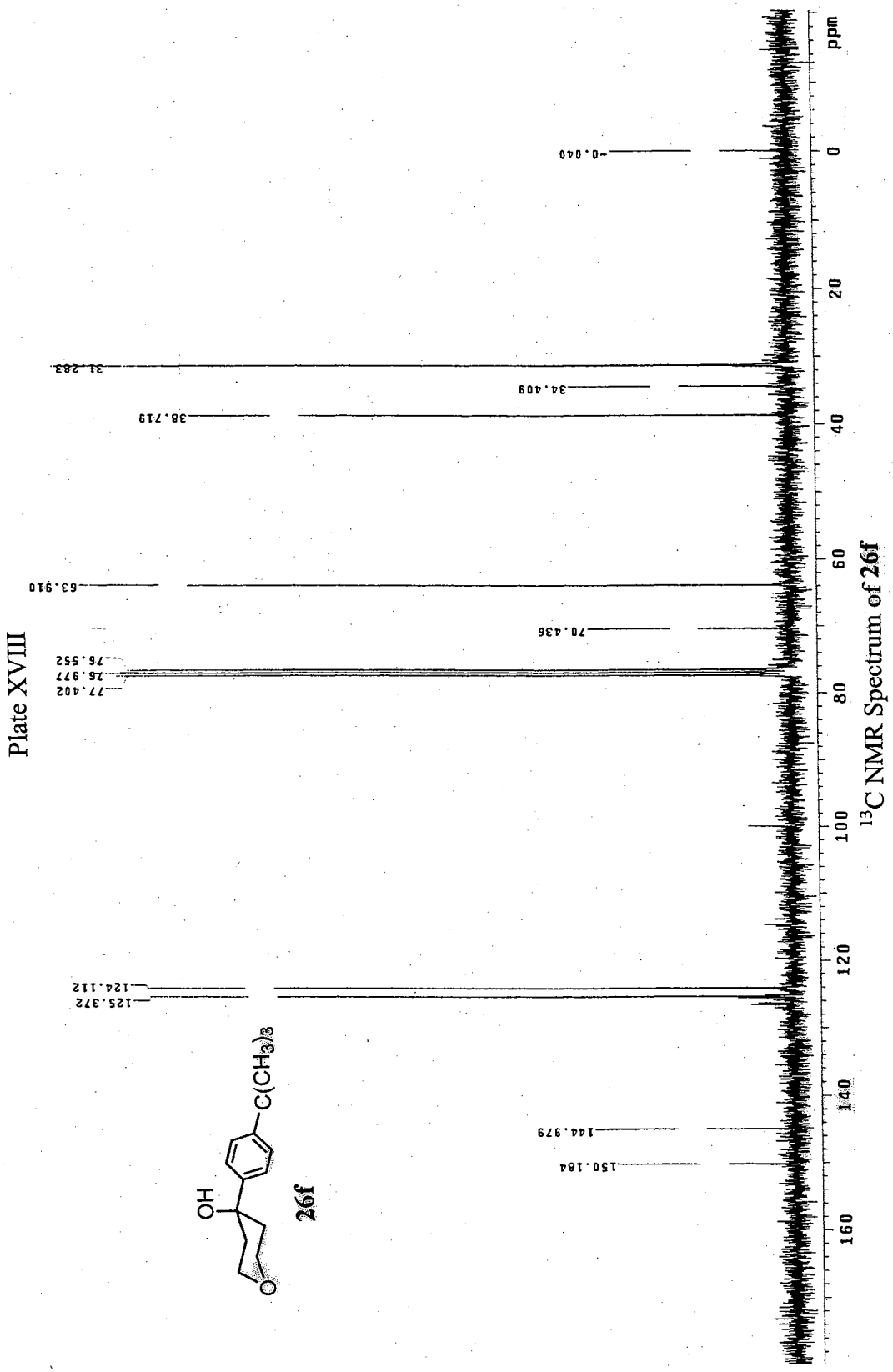
IR Spectrum of **26f**

Plate XVII



^{1}H NMR Spectrum of **26f**

Plate XVIII



26f

^{13}C NMR Spectrum of **26f**

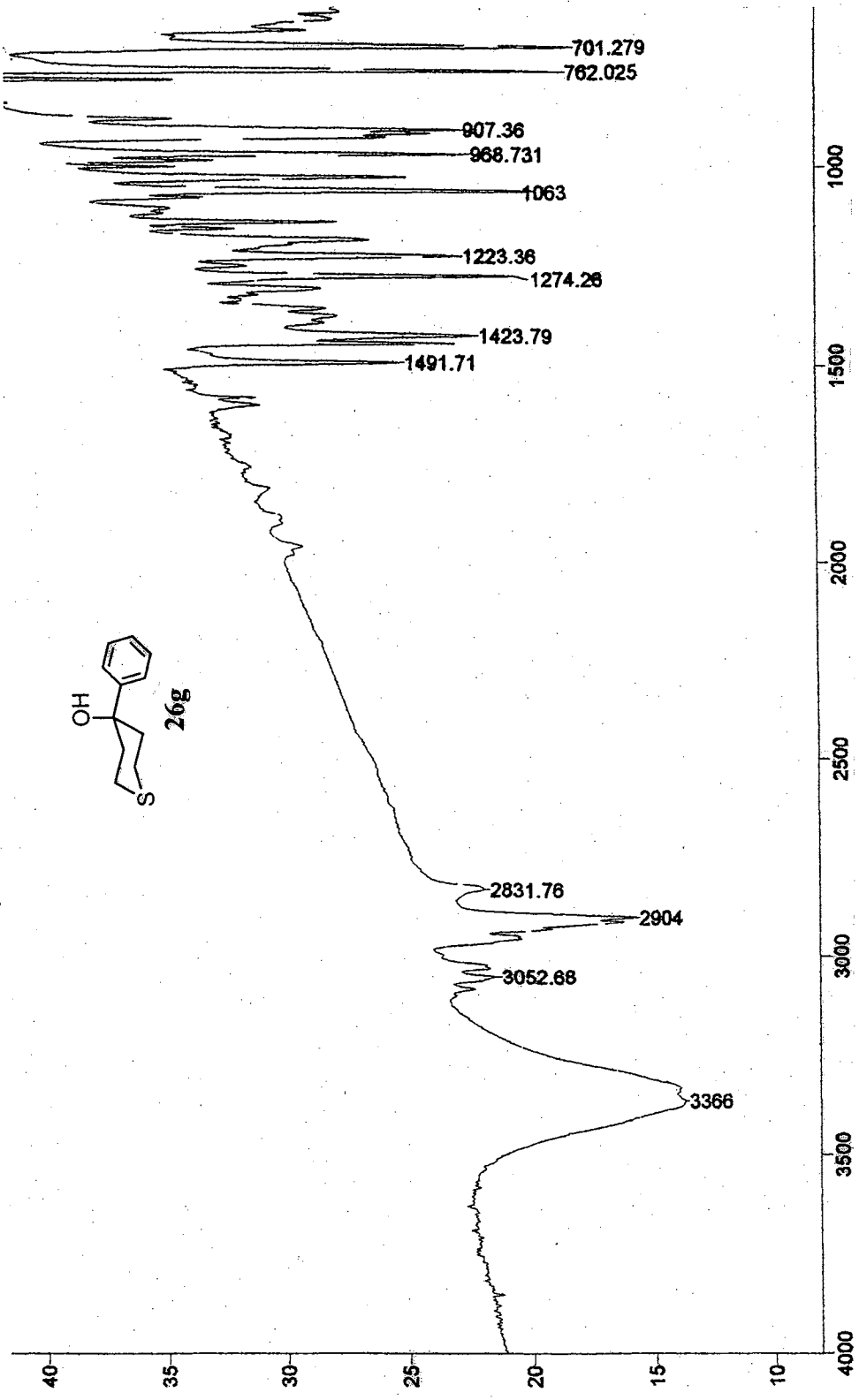
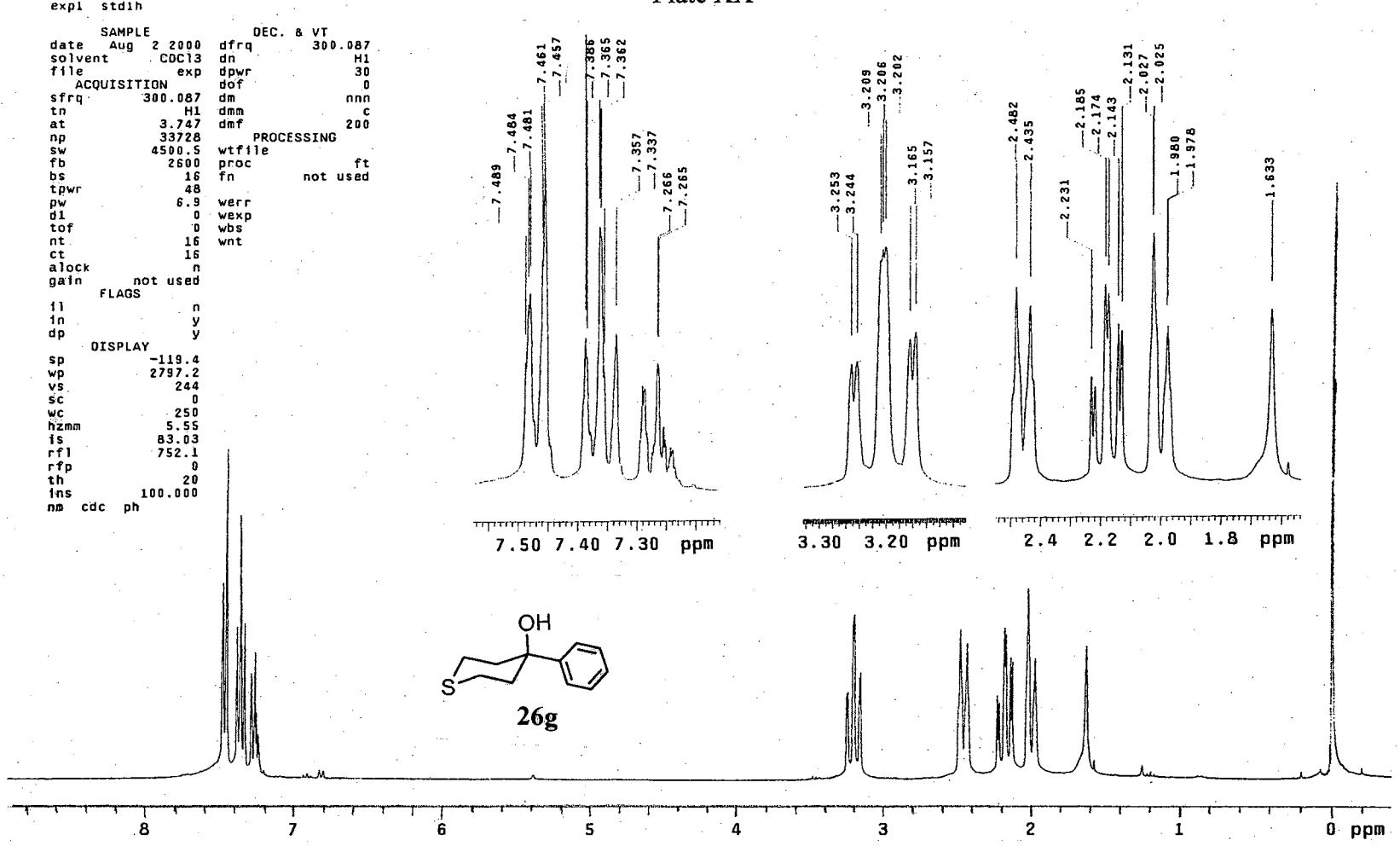


Plate XIX

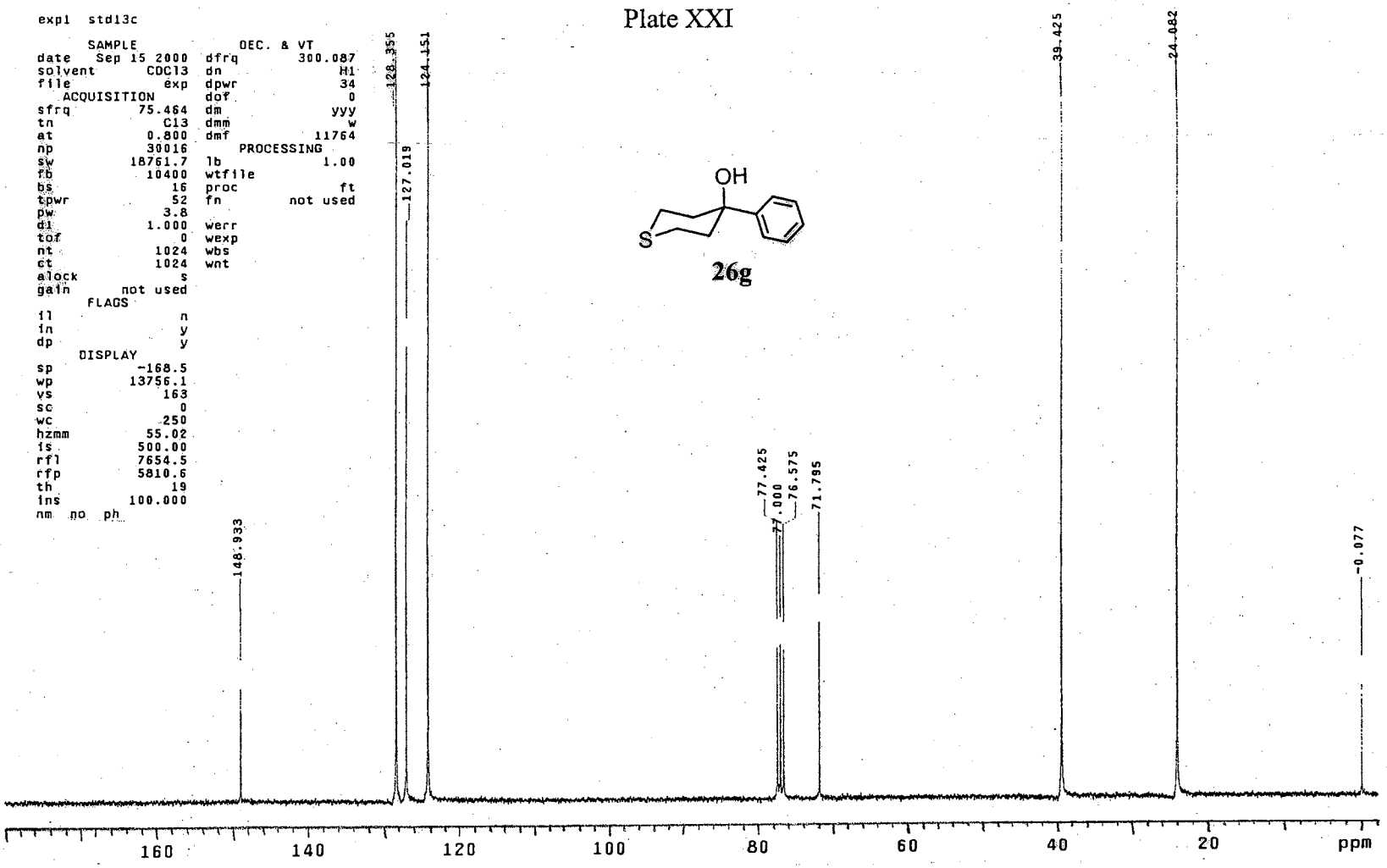
IR Spectrum of **26g**

Plate XX



^{1}H NMR Spectrum of **26g**

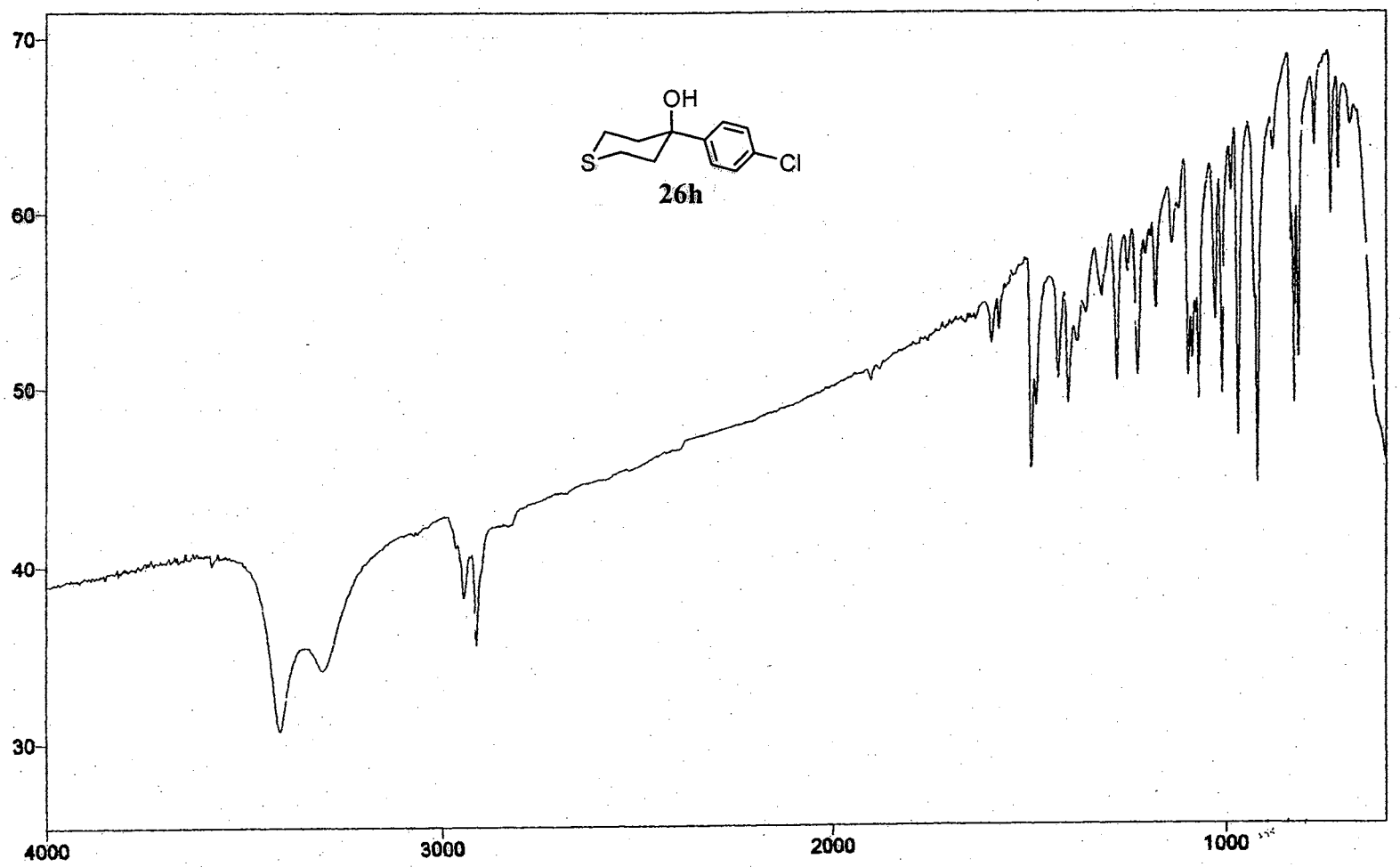
Plate XXI



26g

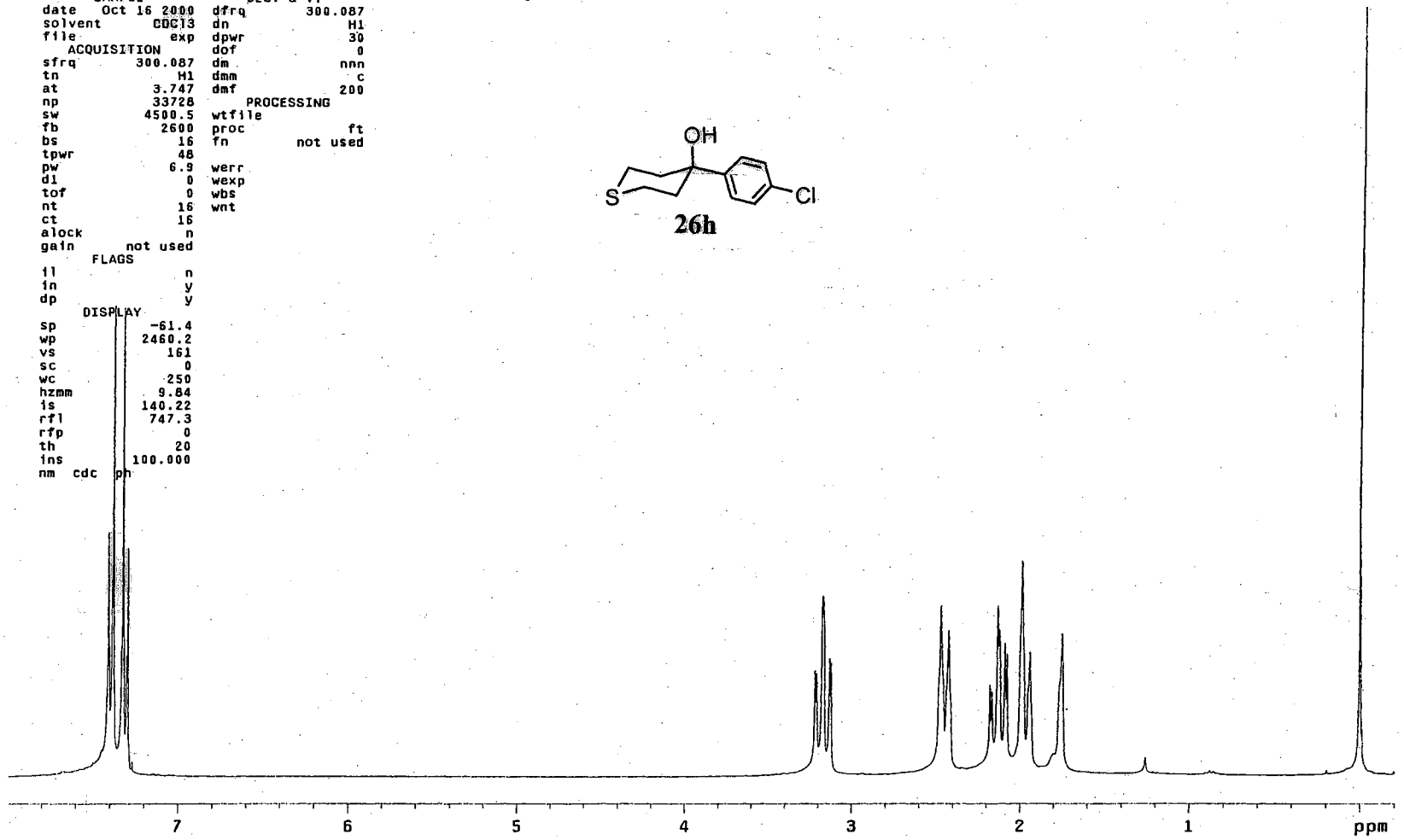
^{13}C NMR Spectrum of **26g**

Plate XXII



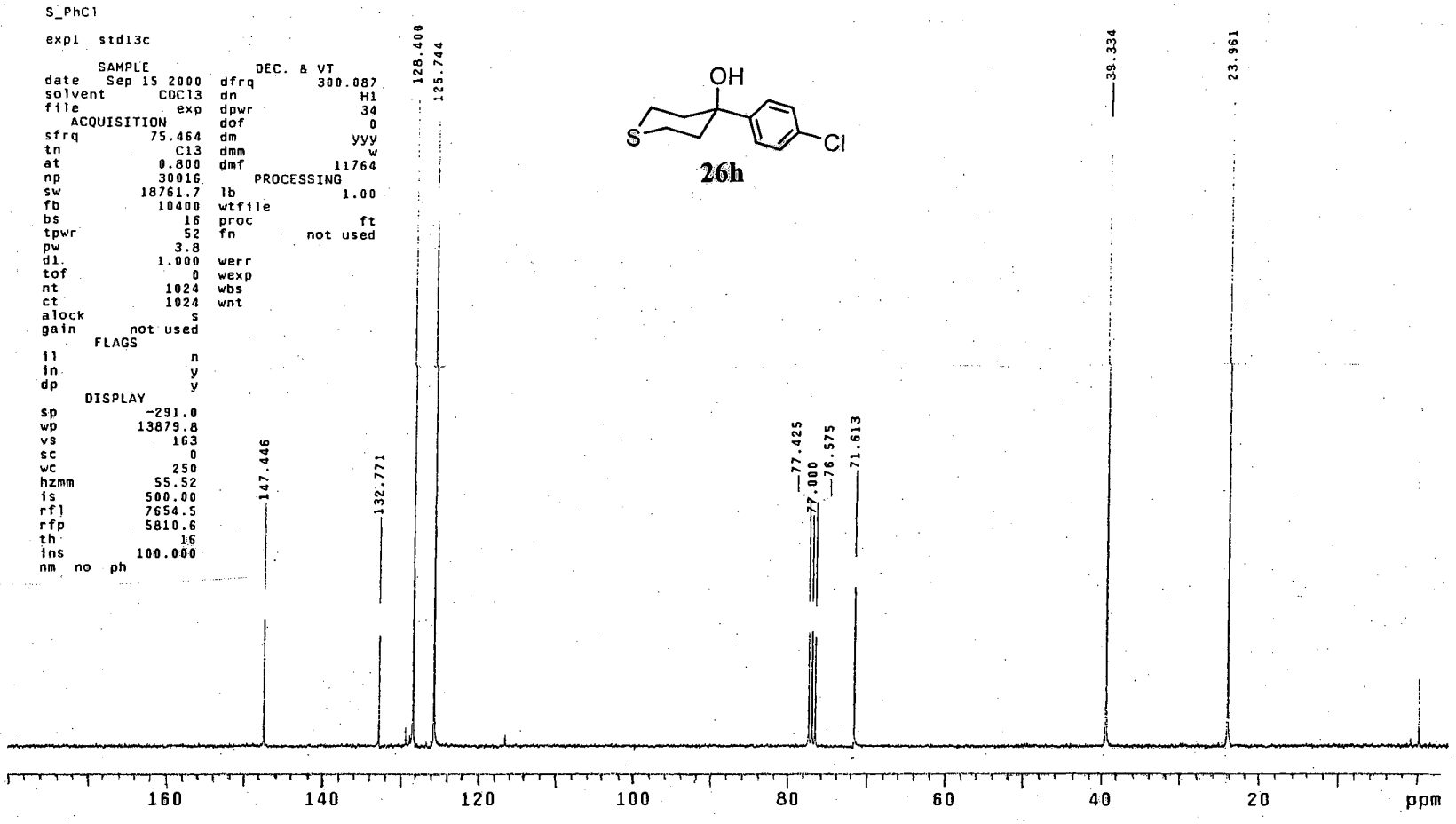
IR Spectrum of **26h**

Plate XXIII



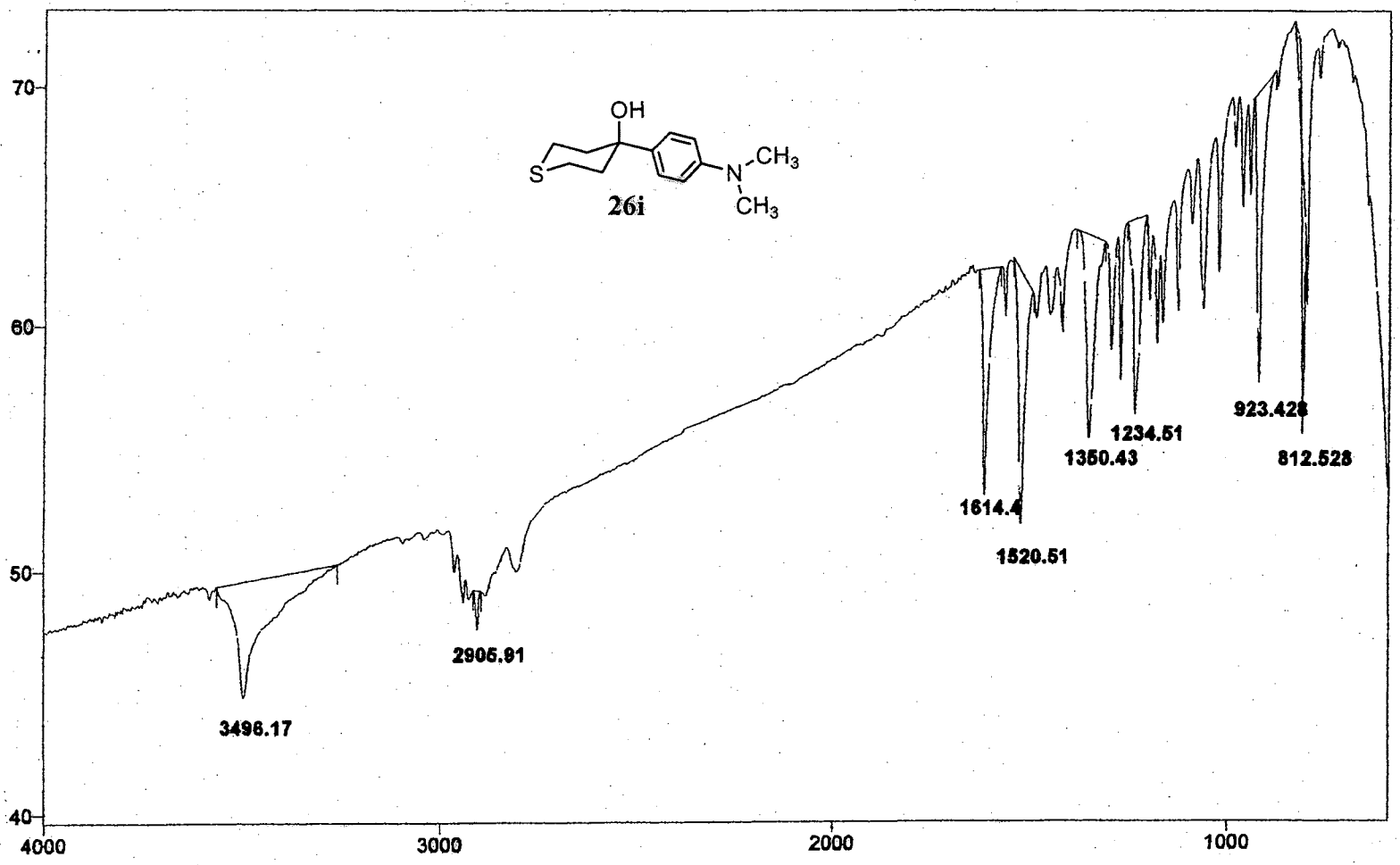
^{1}H NMR Spectrum of **26h**

Plate XXIV



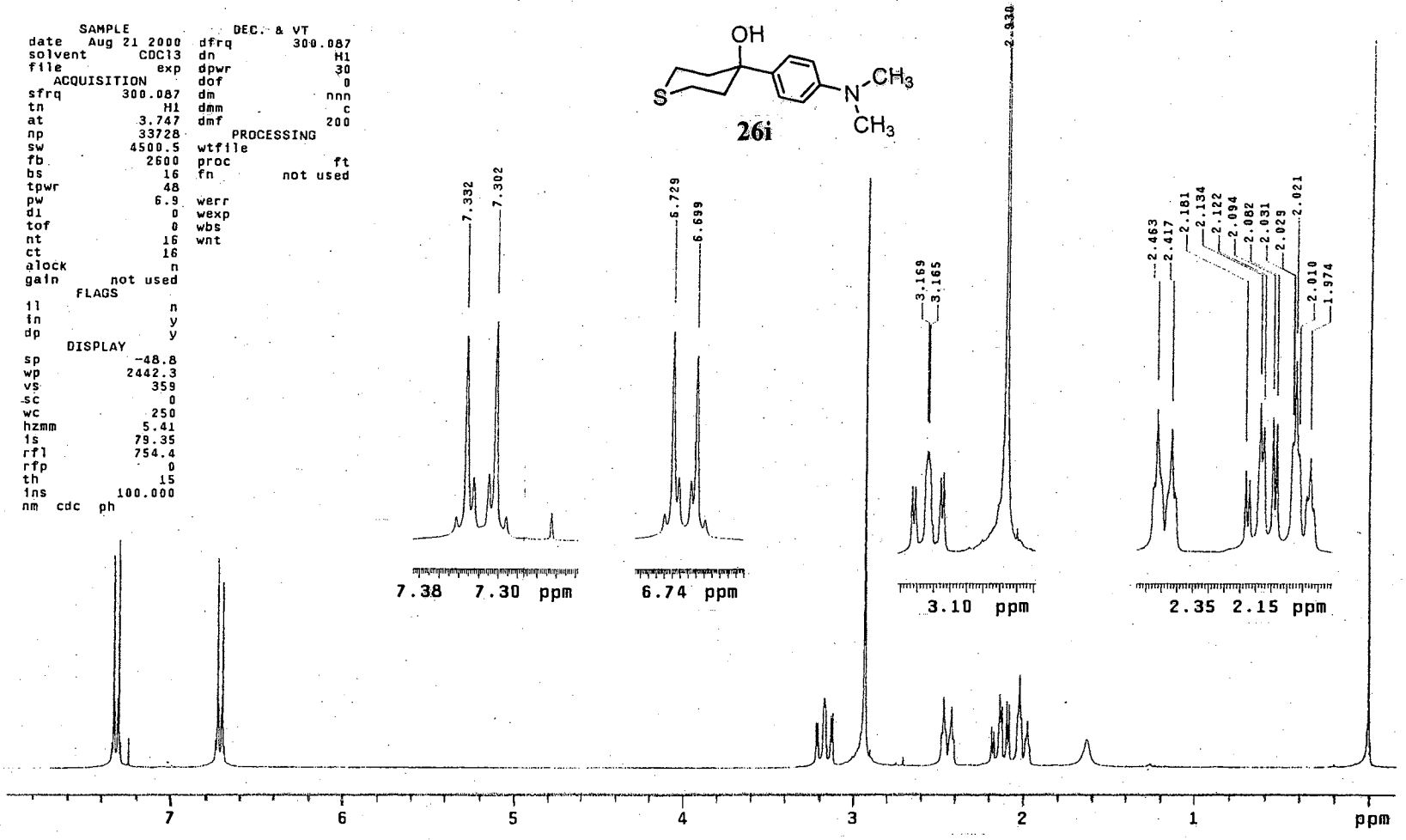
^{13}C NMR Spectrum of **26h**

Plate XXV



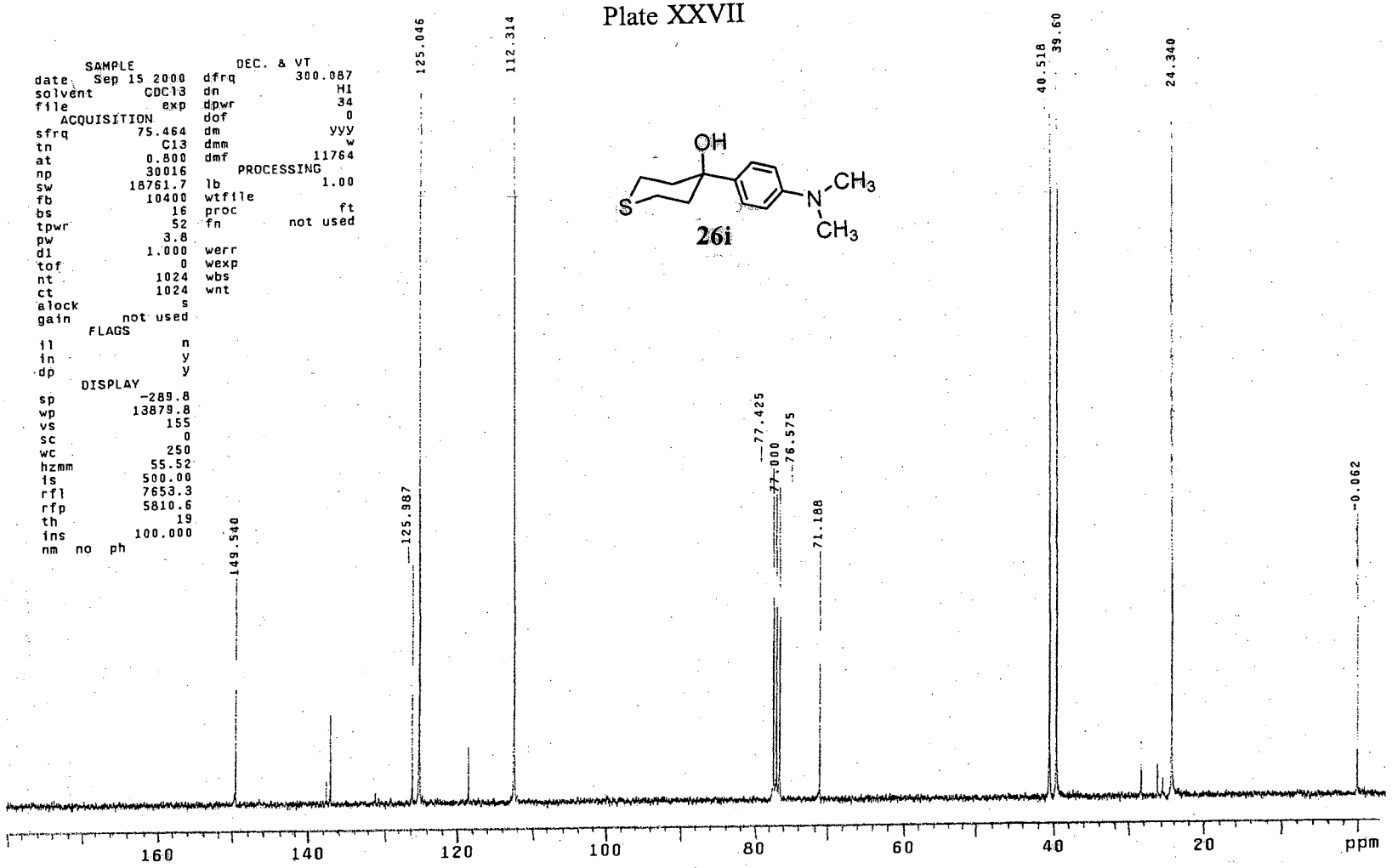
IR Spectrum of **26i**

Plate XXVI



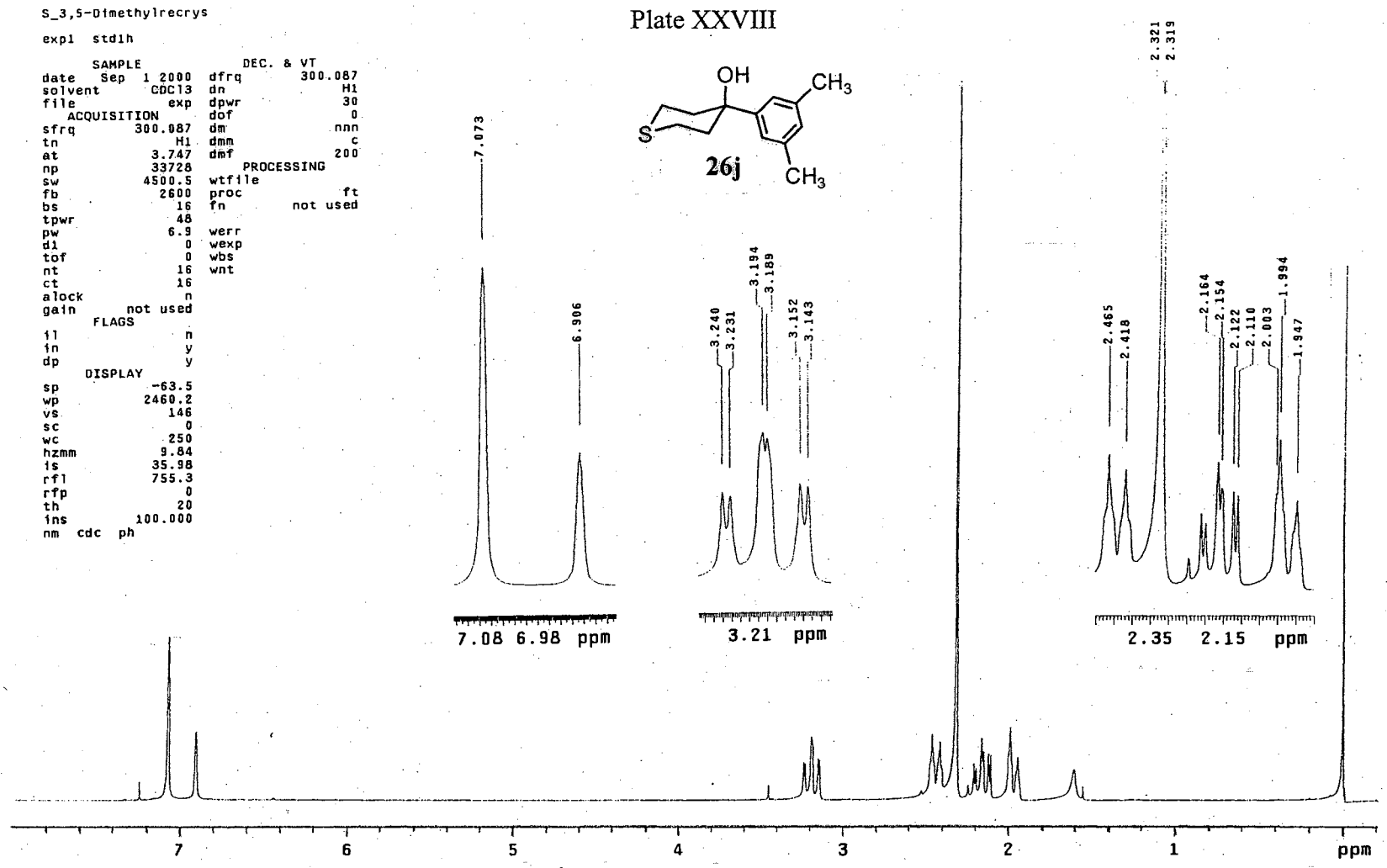
^{1}H NMR Spectrum of **26i**

Plate XXVII



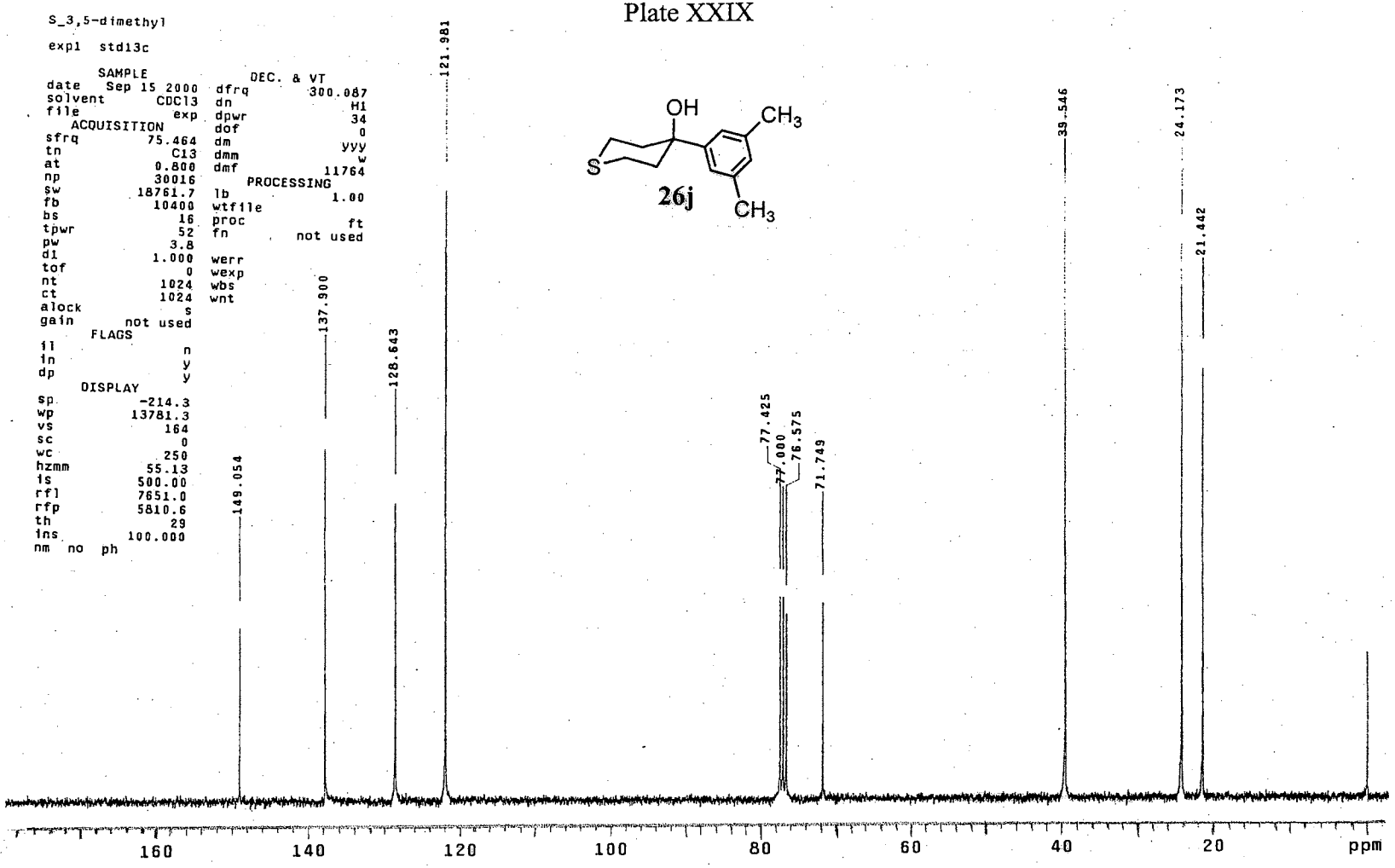
^{13}C NMR Spectrum of **26i**

Plate XXVIII



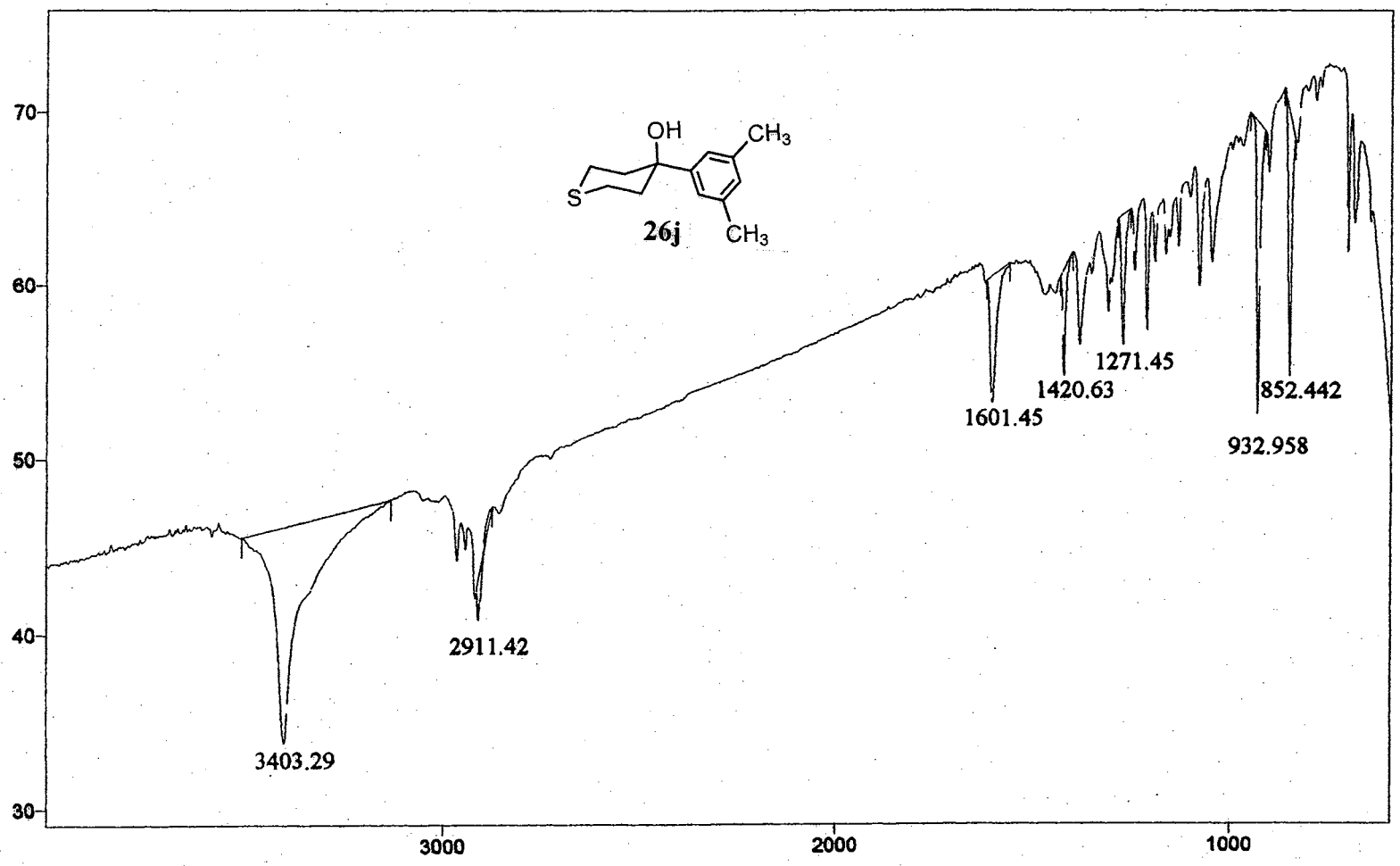
^{1}H NMR Spectrum of **26j**

Plate XXIX



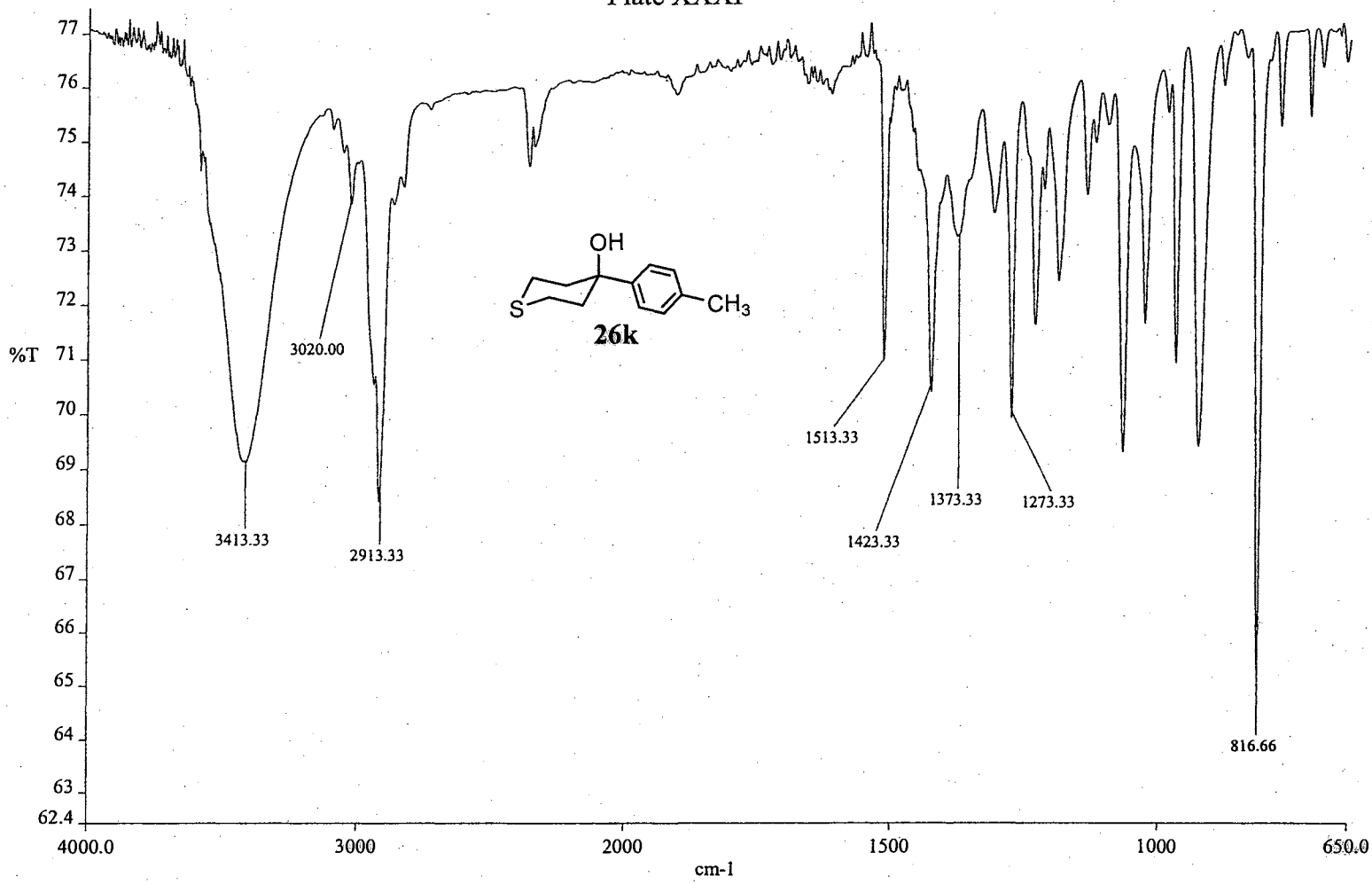
^{13}C NMR Spectrum of **26j**

Plate XXX



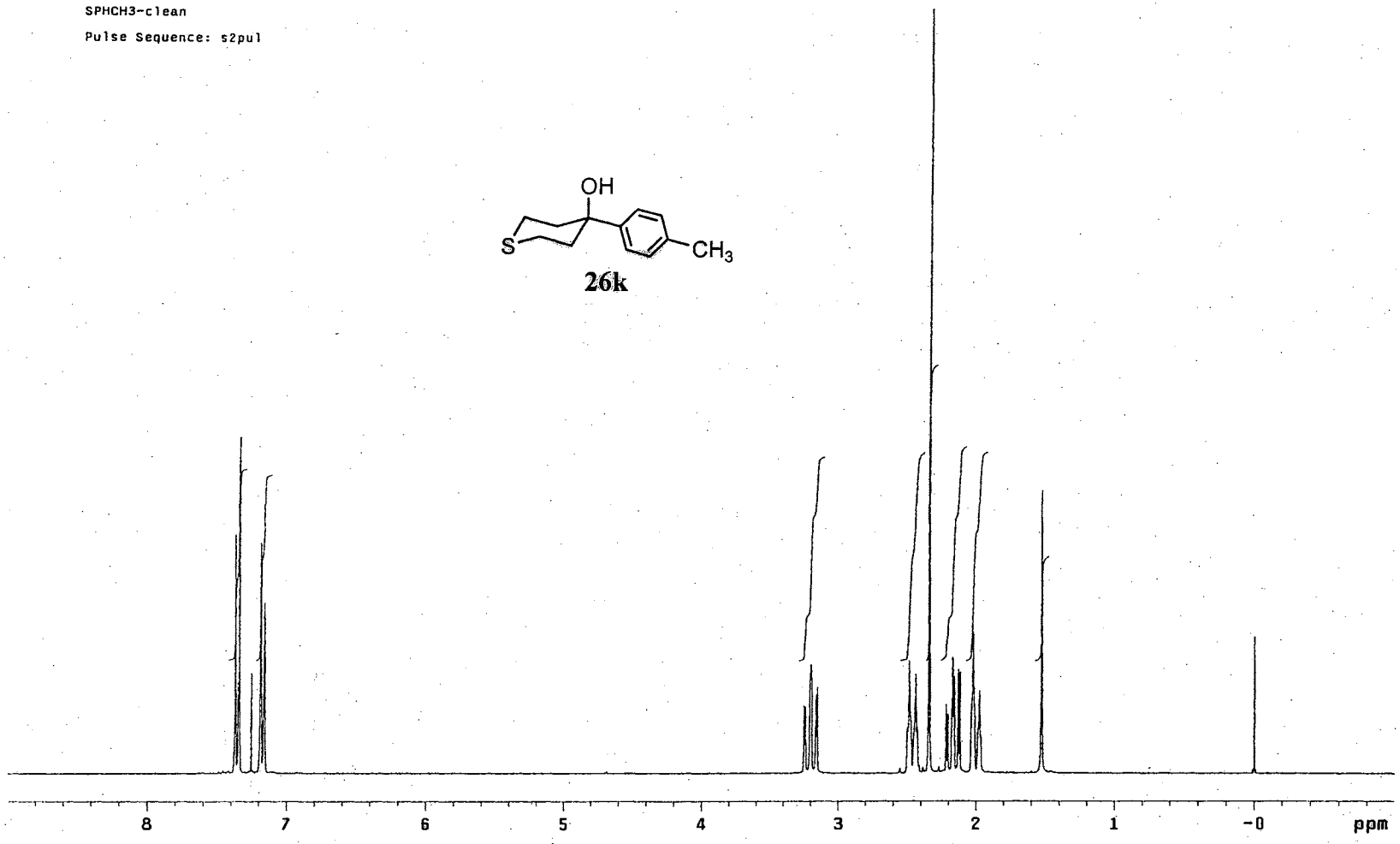
IR Spectrum of **26j**

Plate XXXI



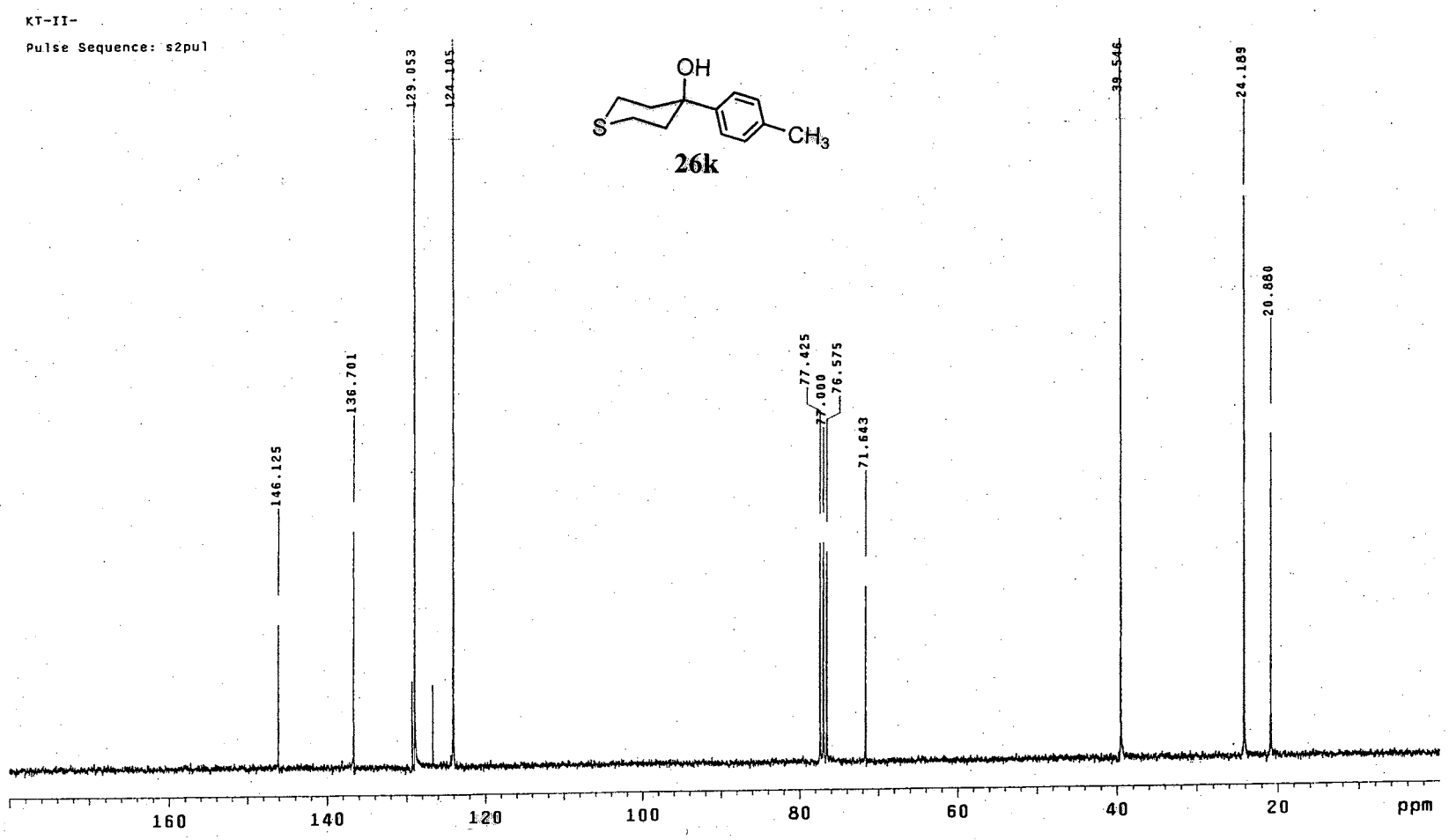
IR Spectrum of **26k**

Plate XXXII



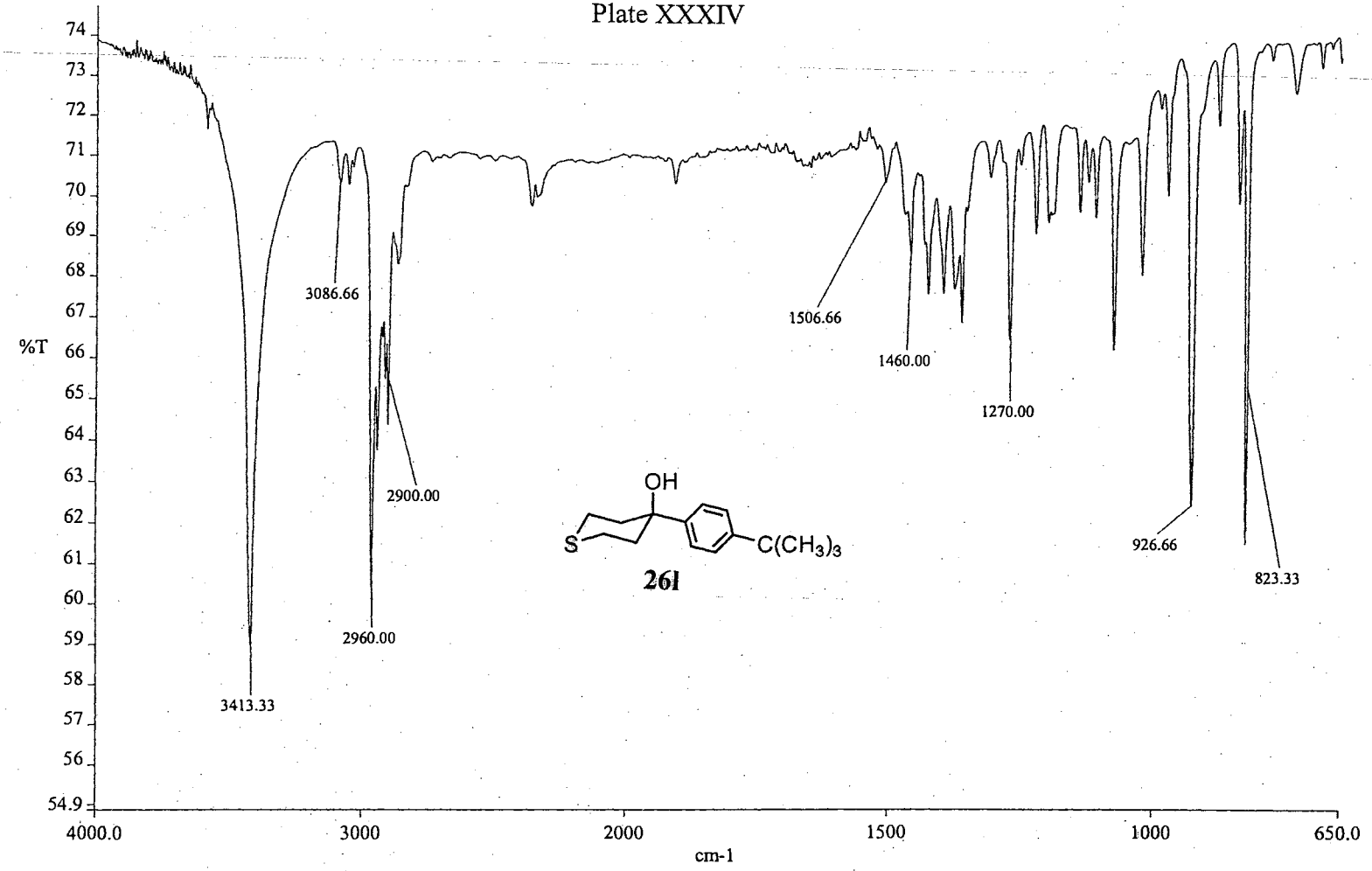
^{1}H NMR Spectrum of **26k**

Plate XXXIII



^{13}C NMR Spectrum of **26k**

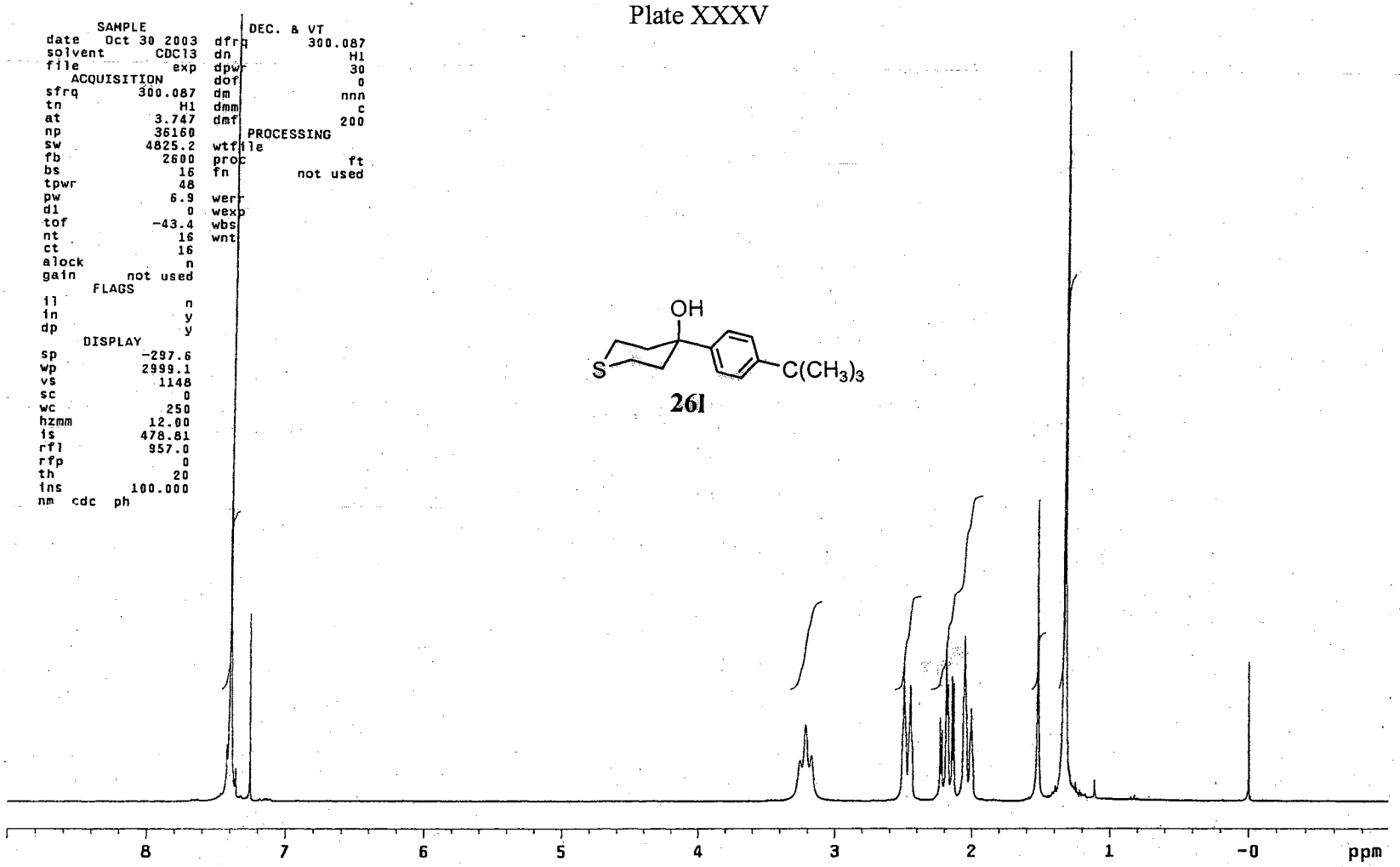
Plate XXXIV



26l

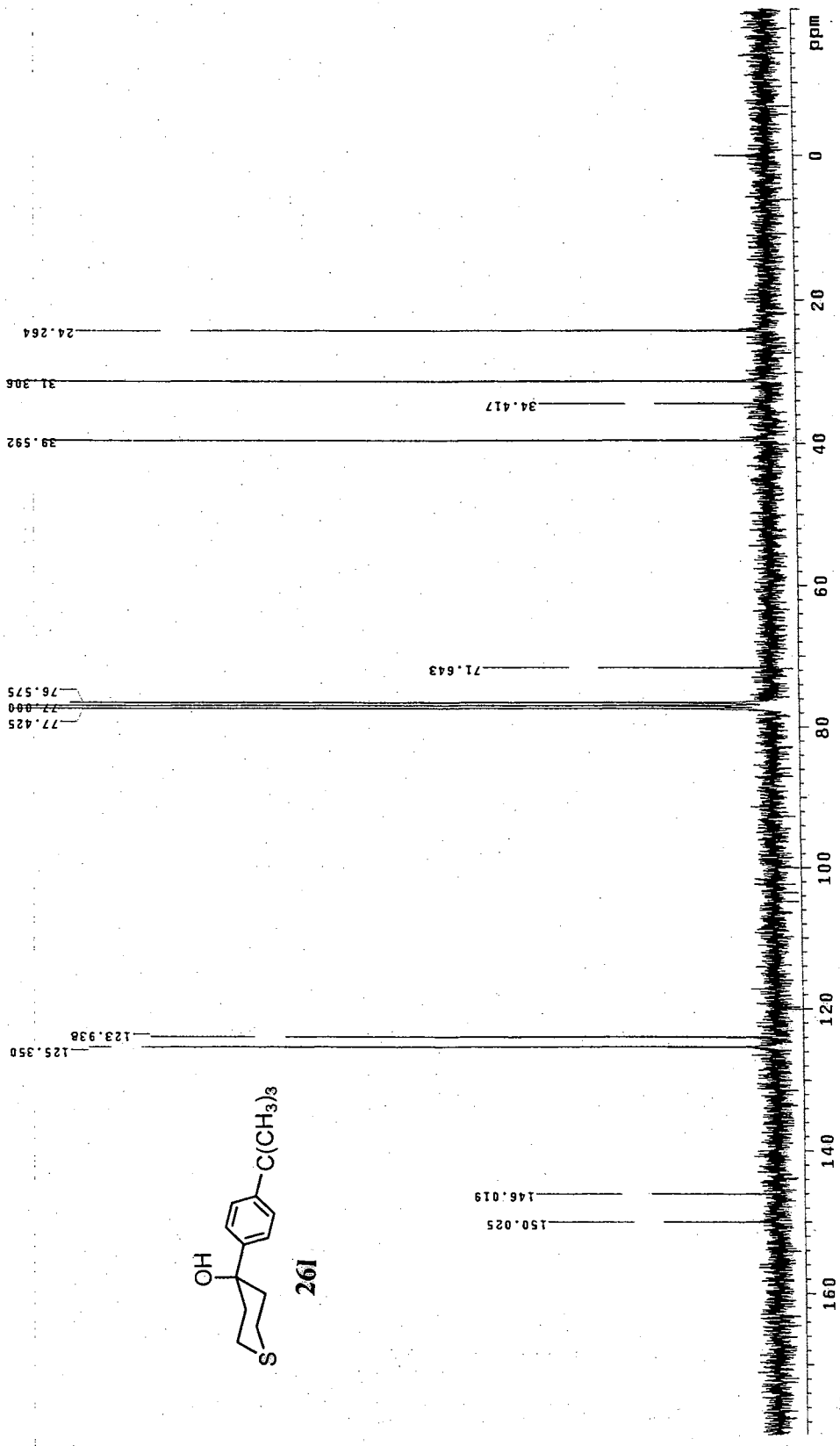
IR Spectrum of **26l**

Plate XXXV



^{1}H NMR Spectrum of **26l**

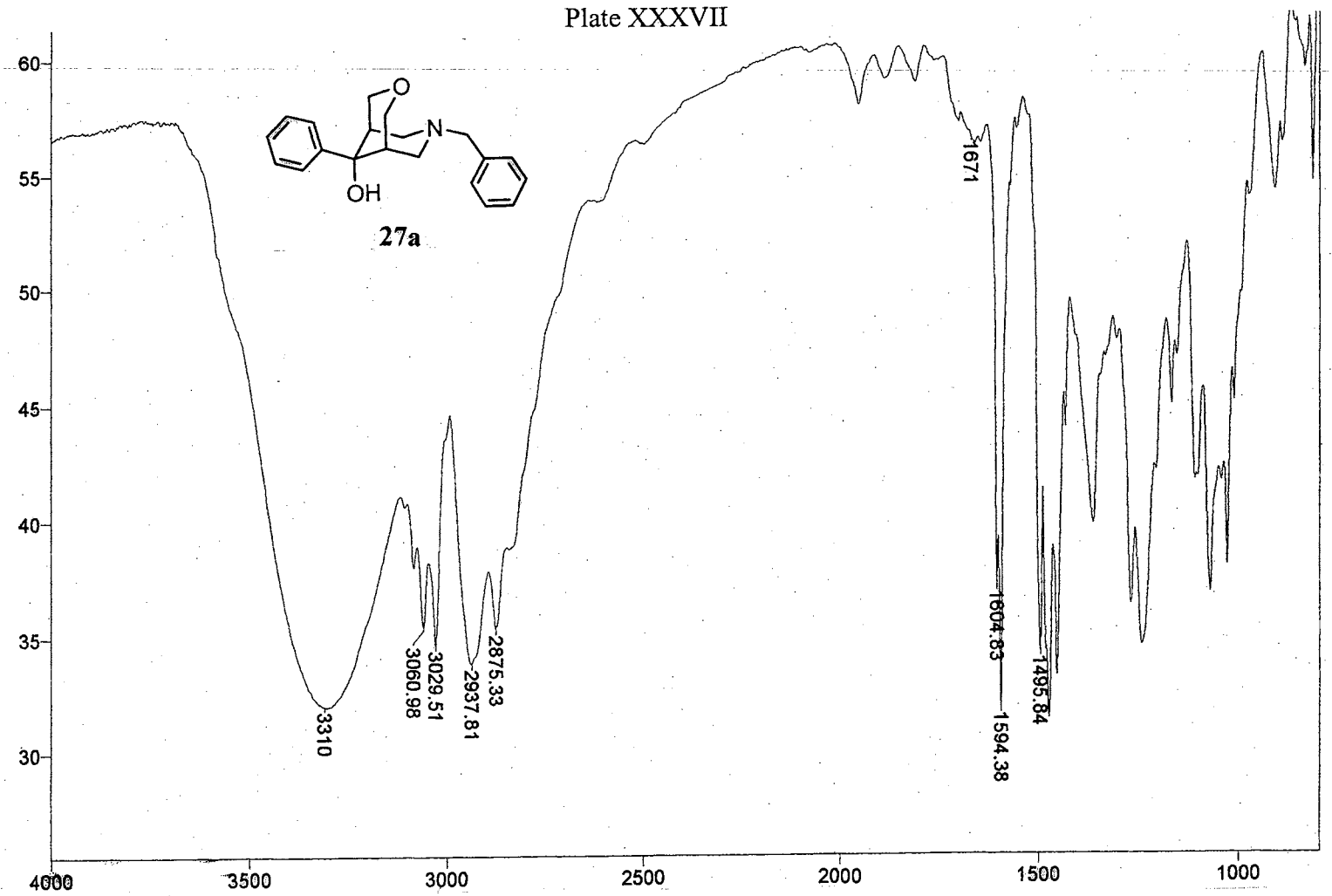
Plate XXXVI



261

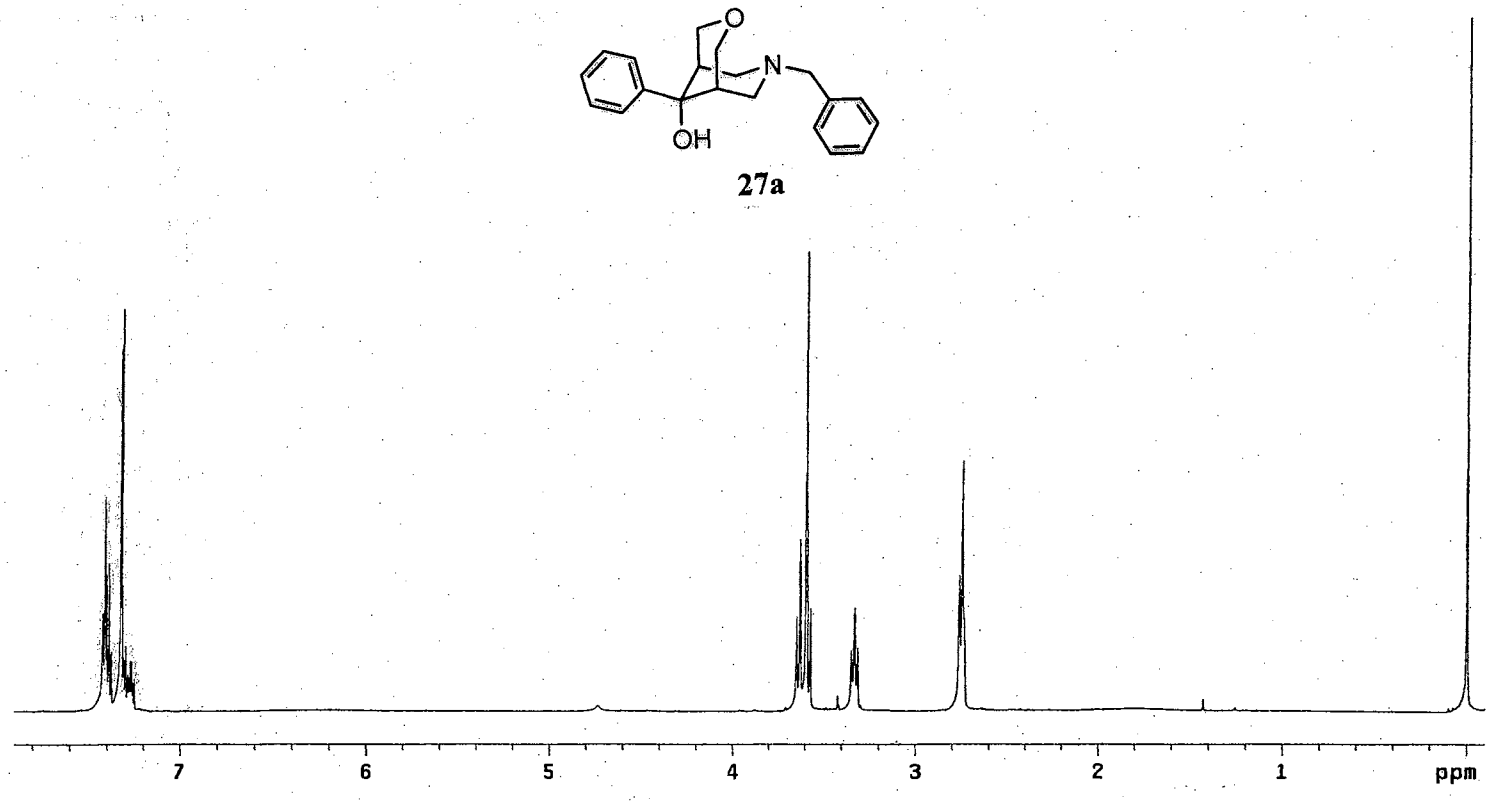
^{13}C NMR Spectrum of **261**

Plate XXXVII



IR Spectrum of **27a**

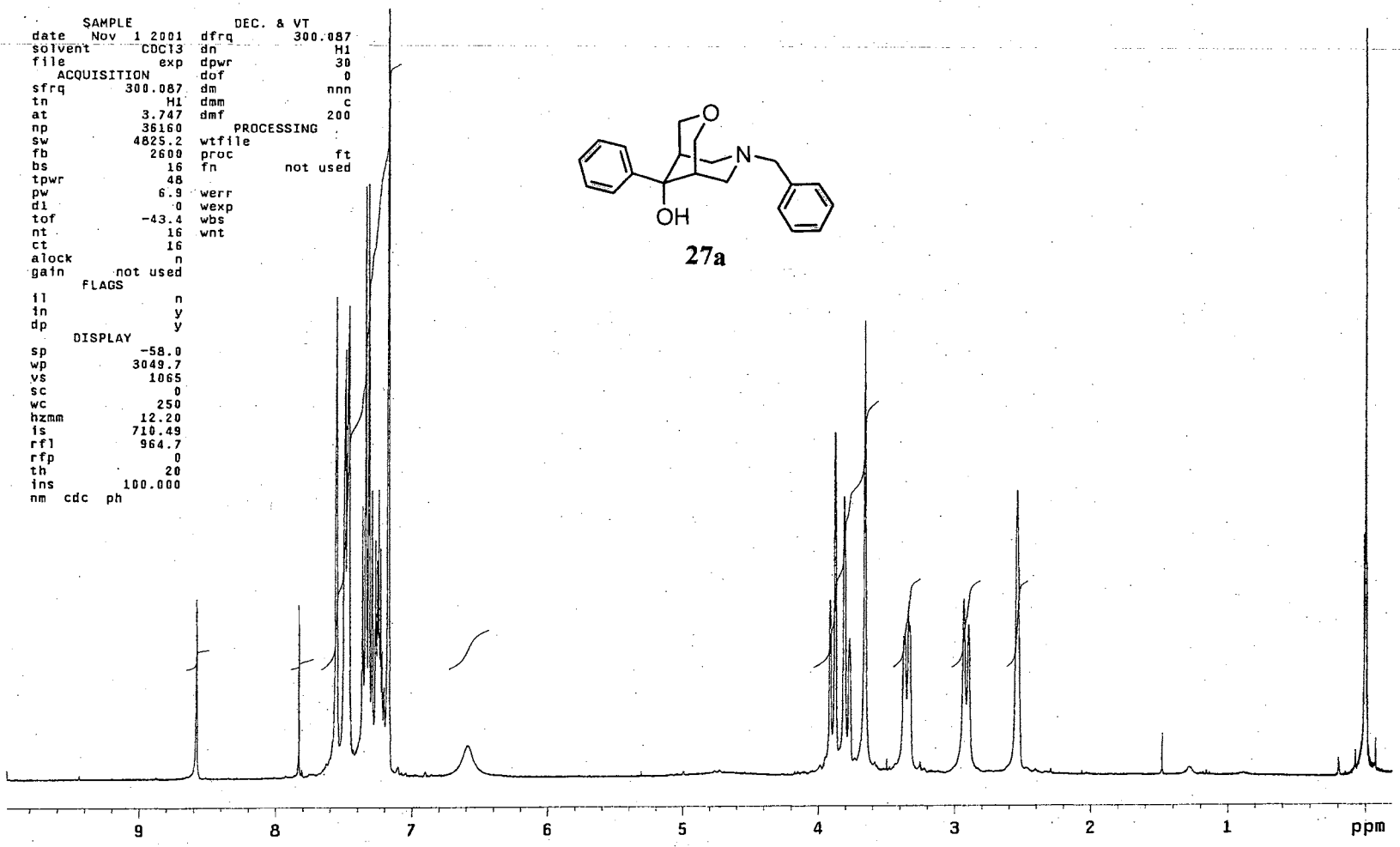
Plate XXXVIII



27a

^{1}H NMR Spectrum of **27a** without pyridine-d_5

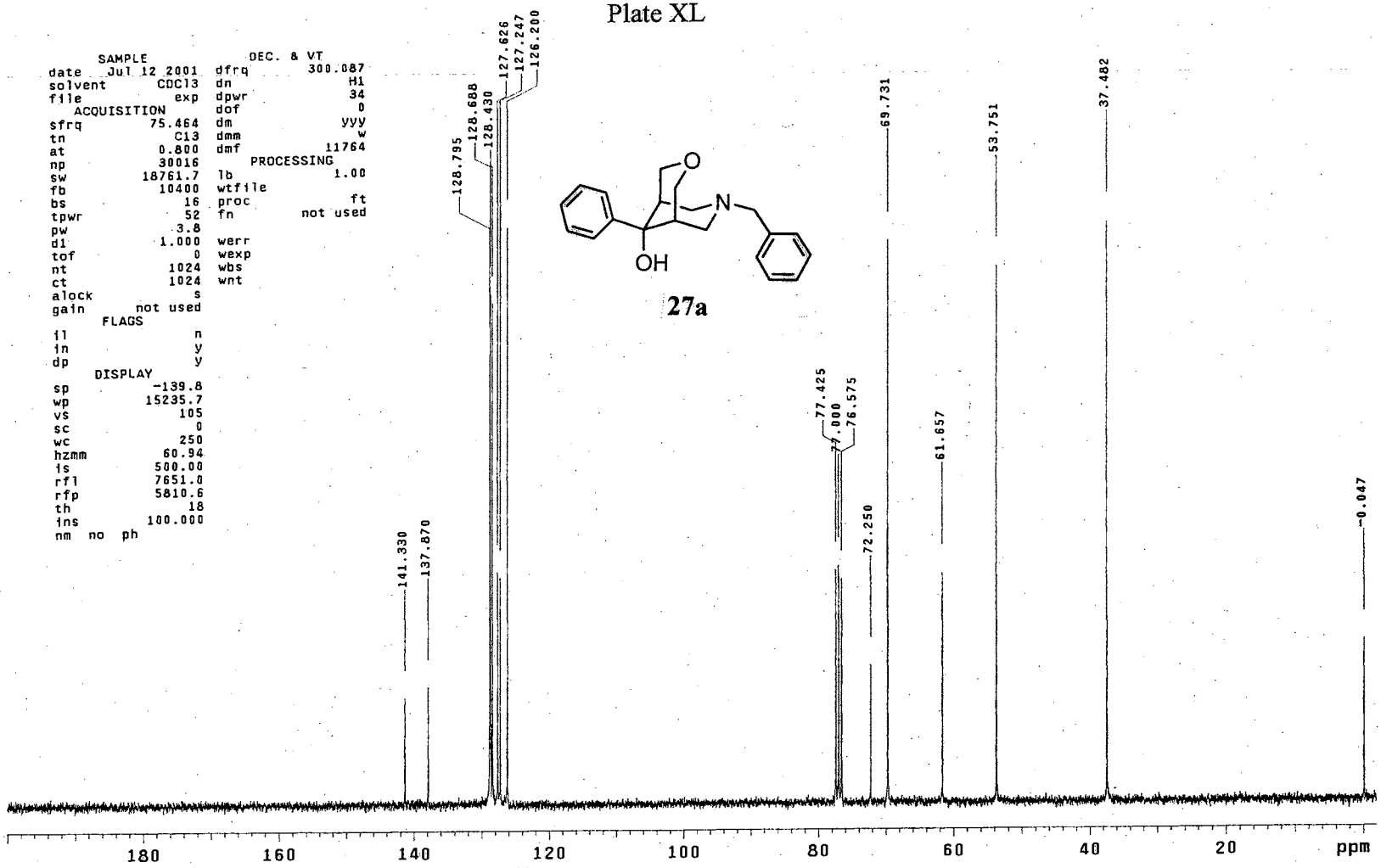
Plate XXXIX



27a

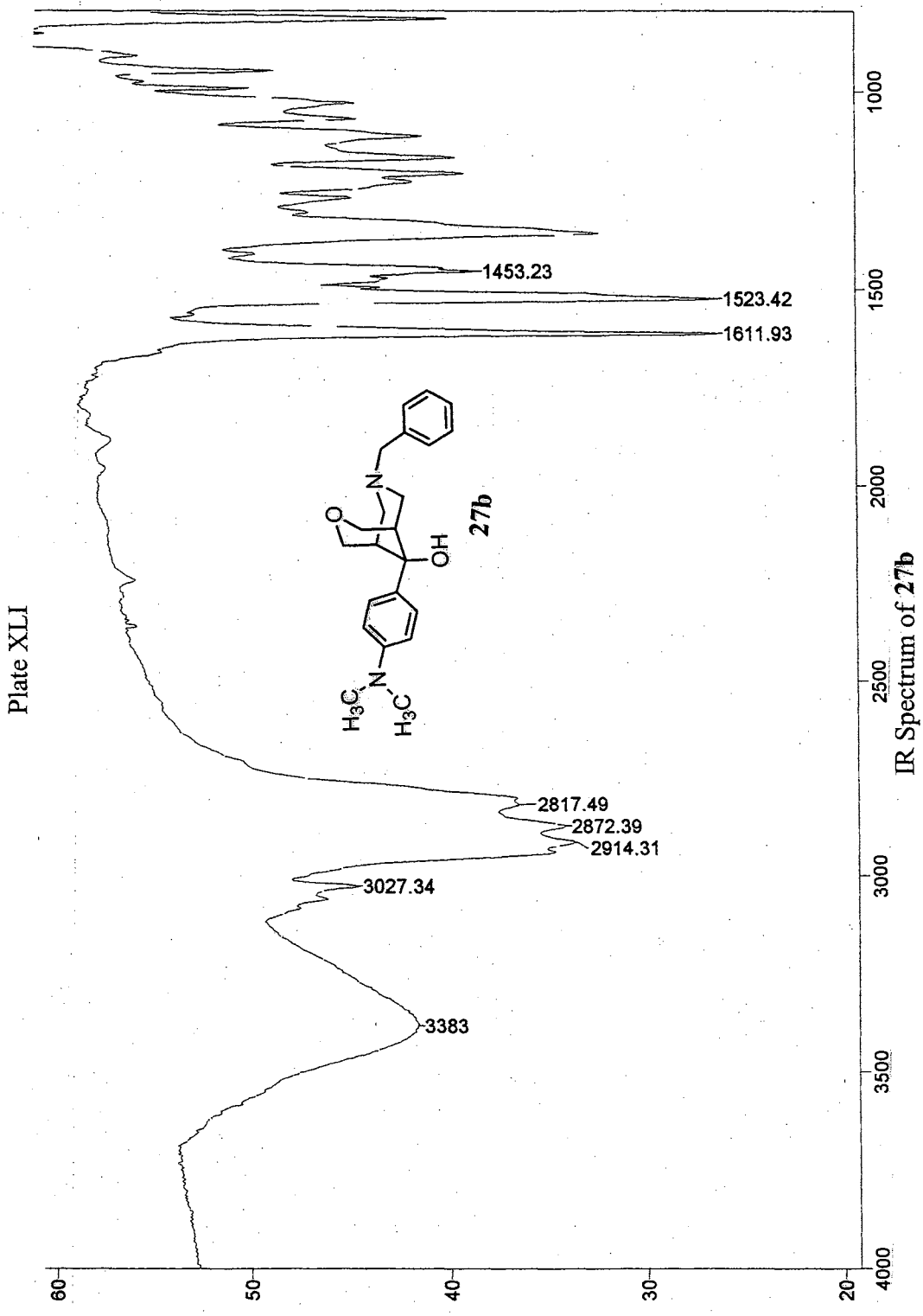
^{1}H NMR Spectrum of **27a** with pyridine-d_5

Plate XL



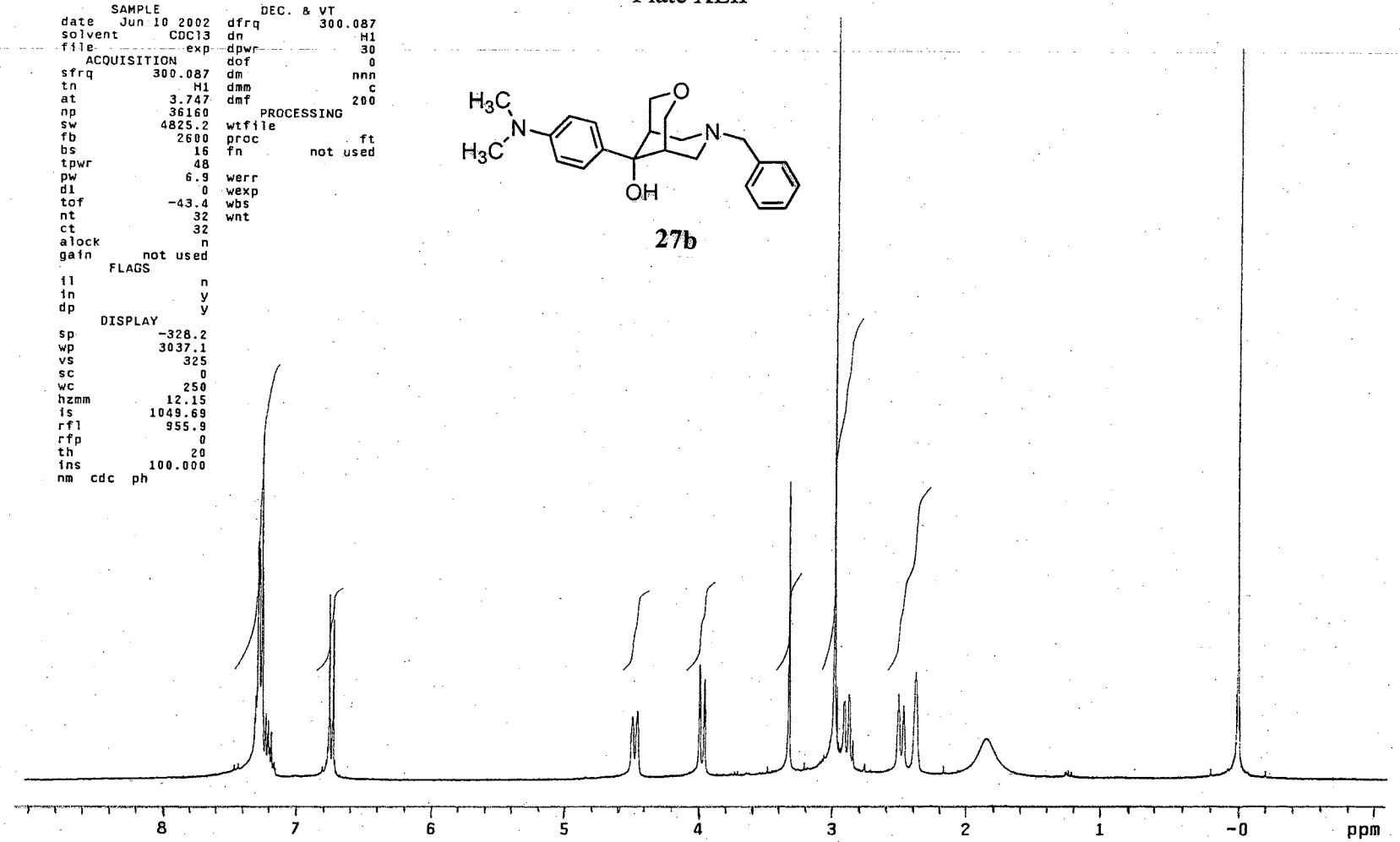
27a

^{13}C NMR Spectrum of **27a**



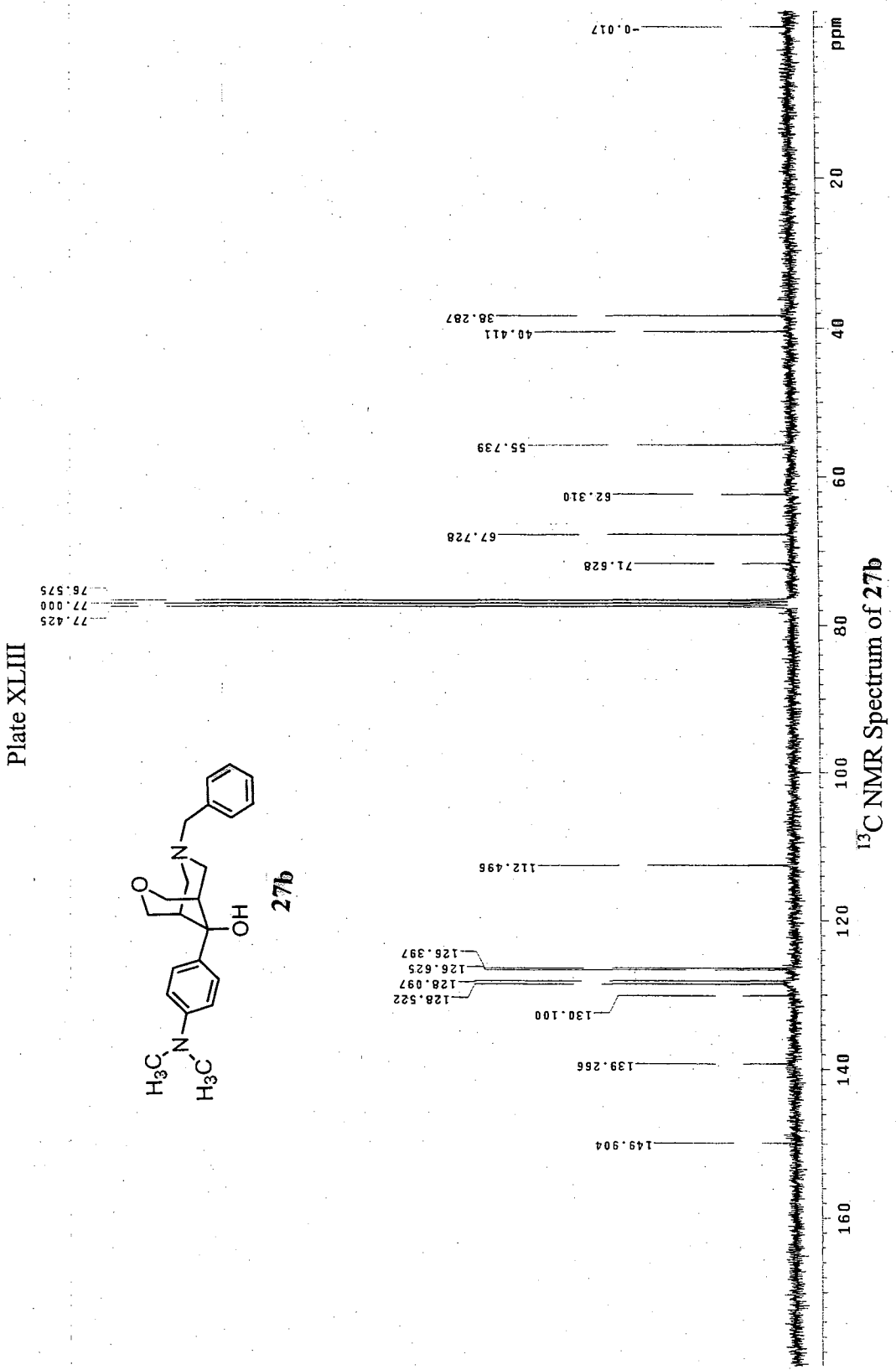
IR Spectrum of **27b**

Plate XLII



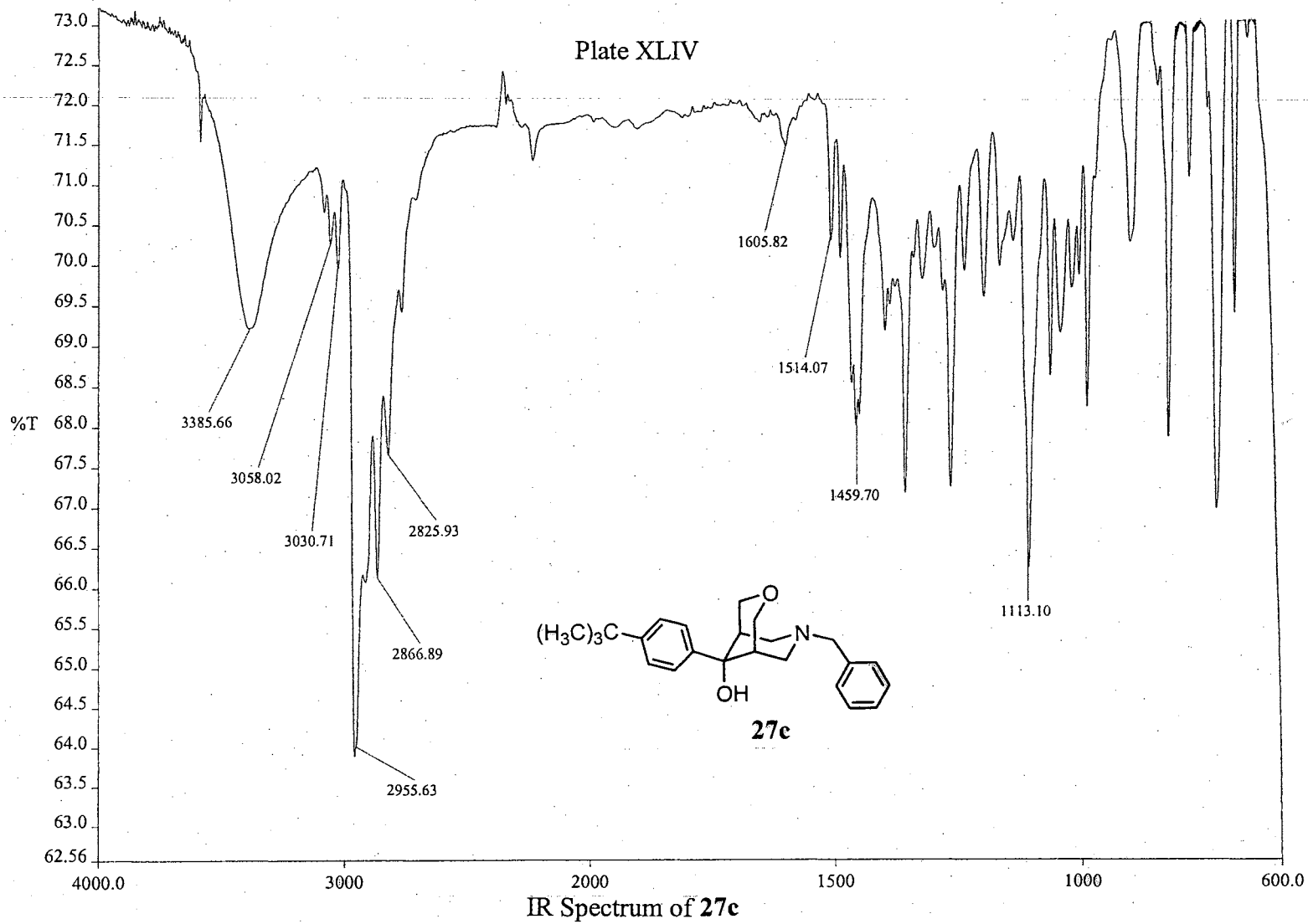
^{1}H NMR Spectrum of **27b**

Plate XLIII



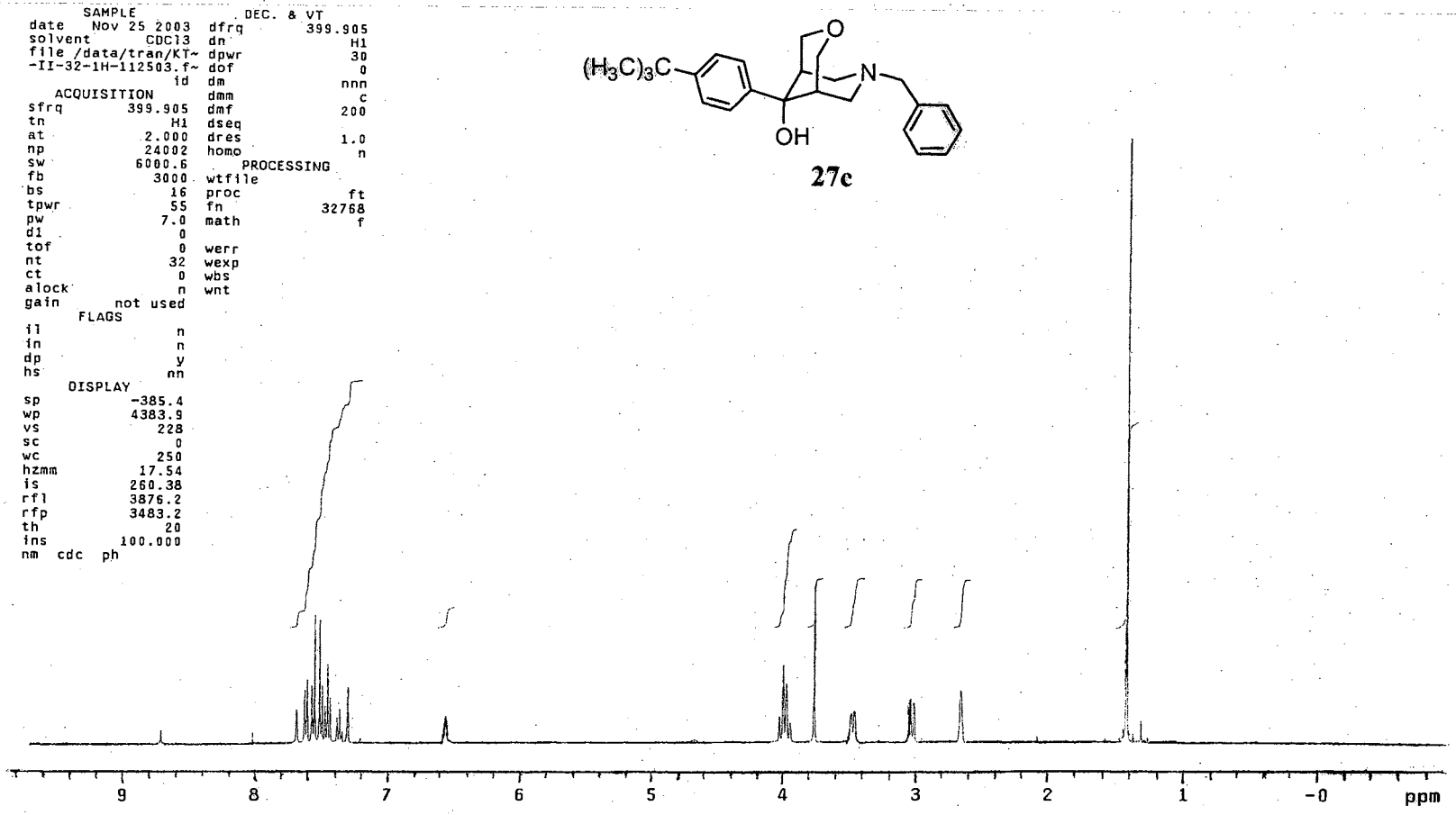
27b

^{13}C NMR Spectrum of **27b**



IR Spectrum of **27c**

Plate XLV



^{1}H NMR Spectrum of **27c**

Plate XLVI

KT-II-33

exp3 std13c

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date	Nov 25 2003	dfrq	399.904
solvent	CDCl3	dn	H1
file	exp	dpwr	35
ACQUISITION		dof	-584.6
sfrq	100.565	dm	nyy
tn	C13	dmm	w
at	1.000	dmf	12000
np	50000	dseq	
sw	25000.0	dres	90.0
fb	14000	homo	n
bs	16	PROCESSING	
tpwr	53	lb	1.50
pw	7.4	wtfile	
d1	1.000	proc	ft
d2	0.500	fn	65536
tof	0	math	f
nt	1024		
ct	0	werr	
alock	n	wexp	
gain	56	wbs	
FLAGS		wnt	
il	n		
in	n		
dp	y		
hs	nn		
DISPLAY			
sp	-2971.7		
wp	21057.8		
vs	2150		
sc	0		
wc	250		
hzmm	84.23		
is	500.00		
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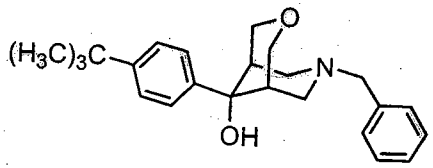
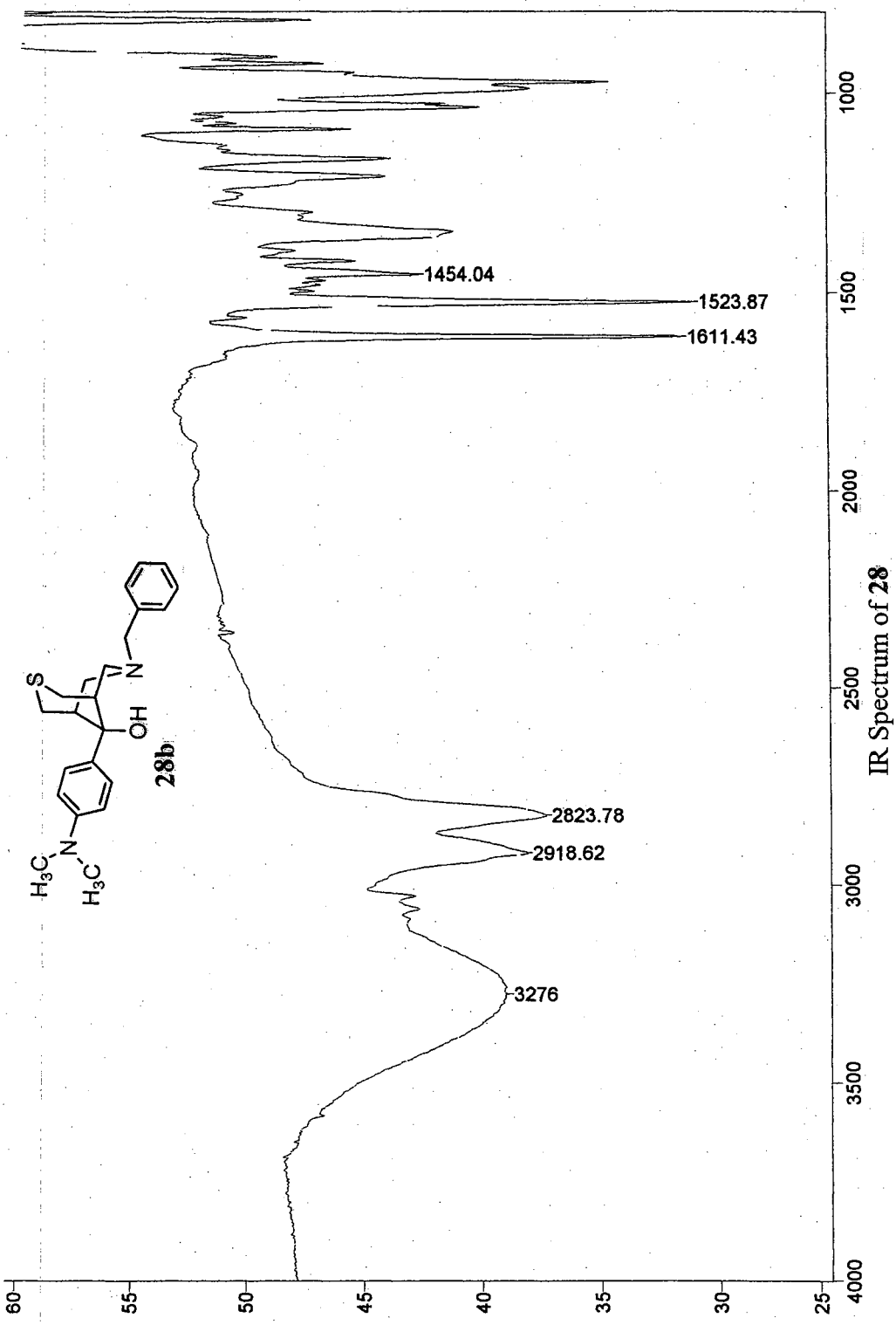
rfp	7743.4		
th	21		
ins	100.000		
ai no ph			



27c

^{13}C NMR Spectrum of **27c**

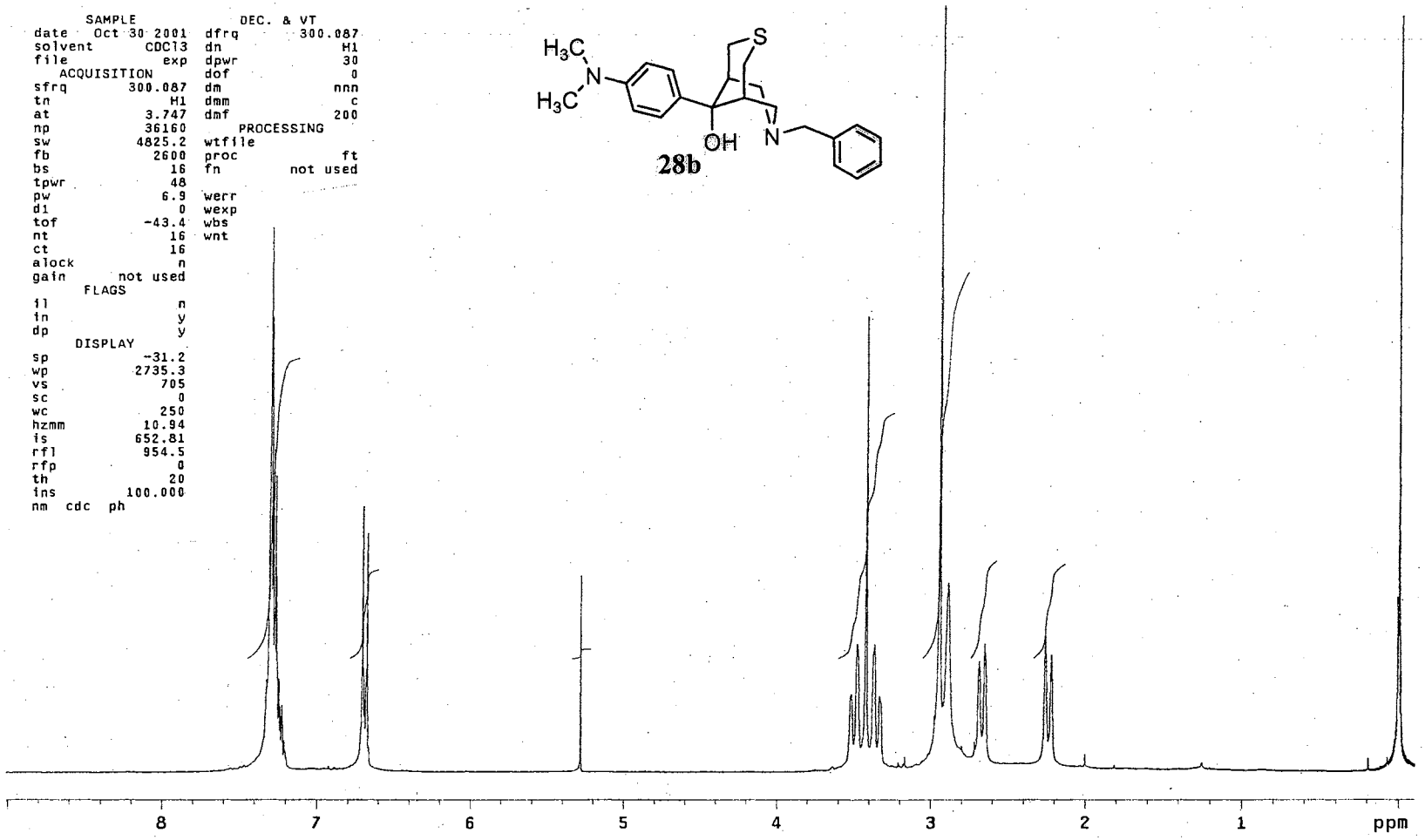
Plate XLVII



28b

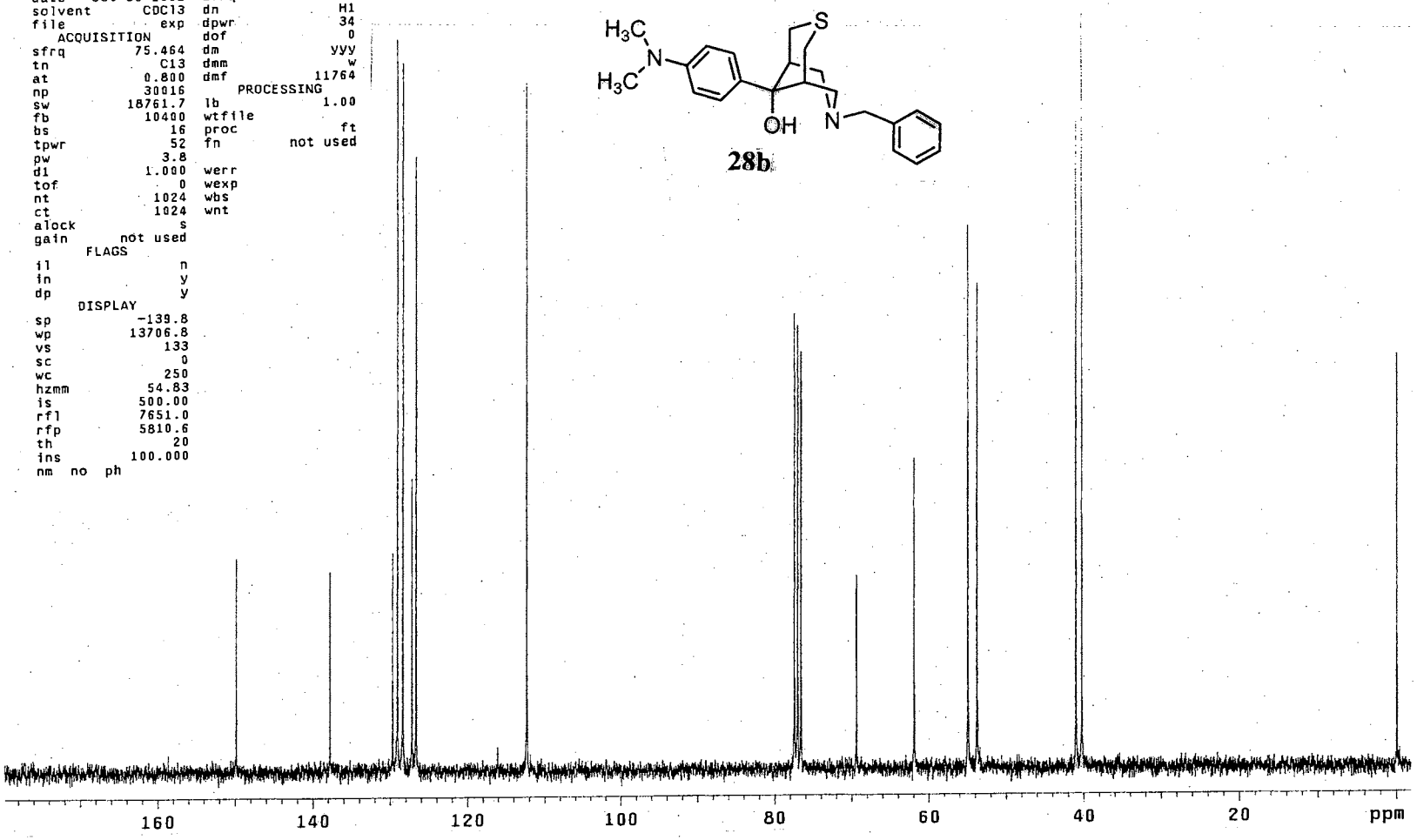
IR Spectrum of **28**

Plate XLVIII



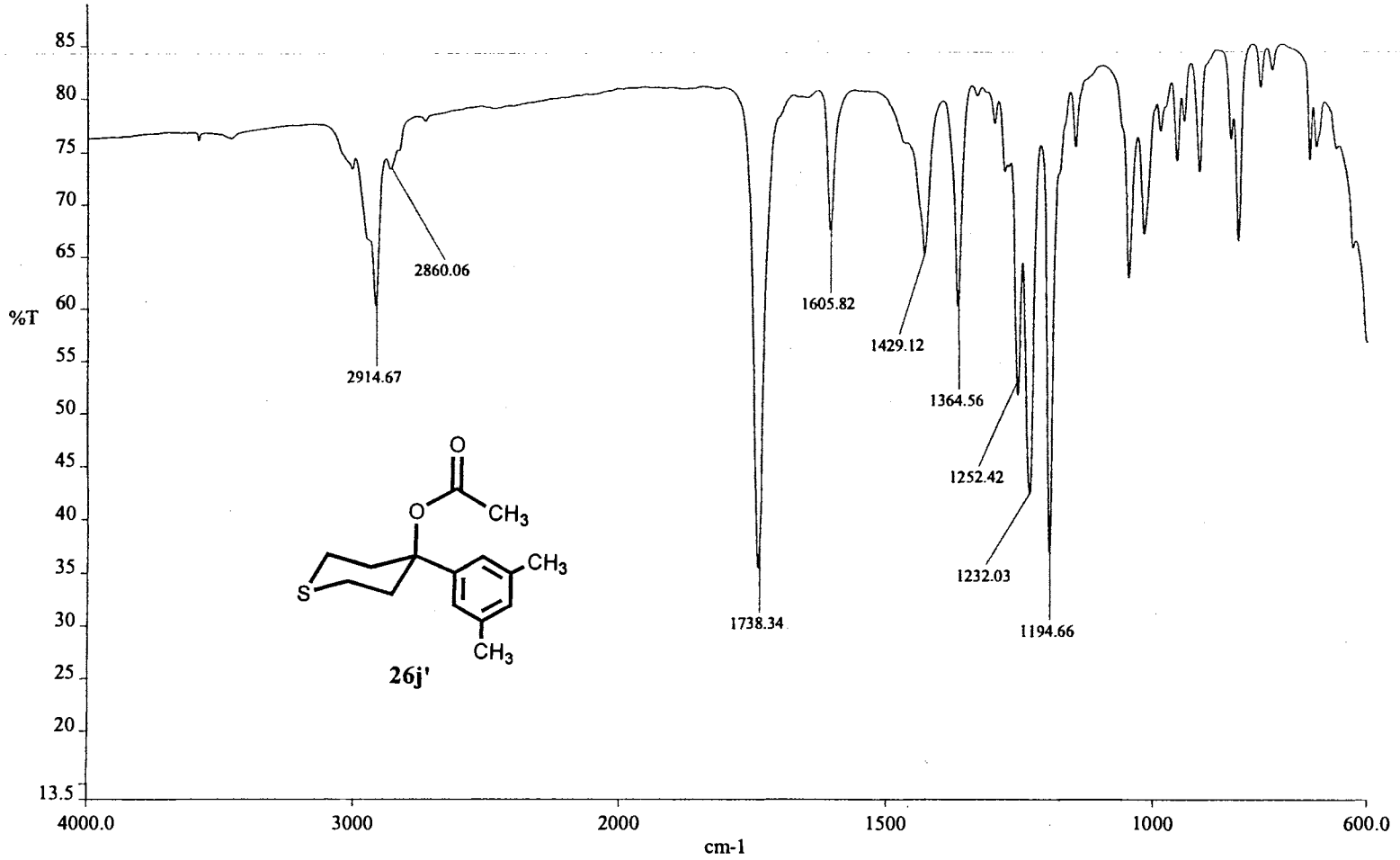
^{1}H NMR Spectrum of **28**

Plate XLIX



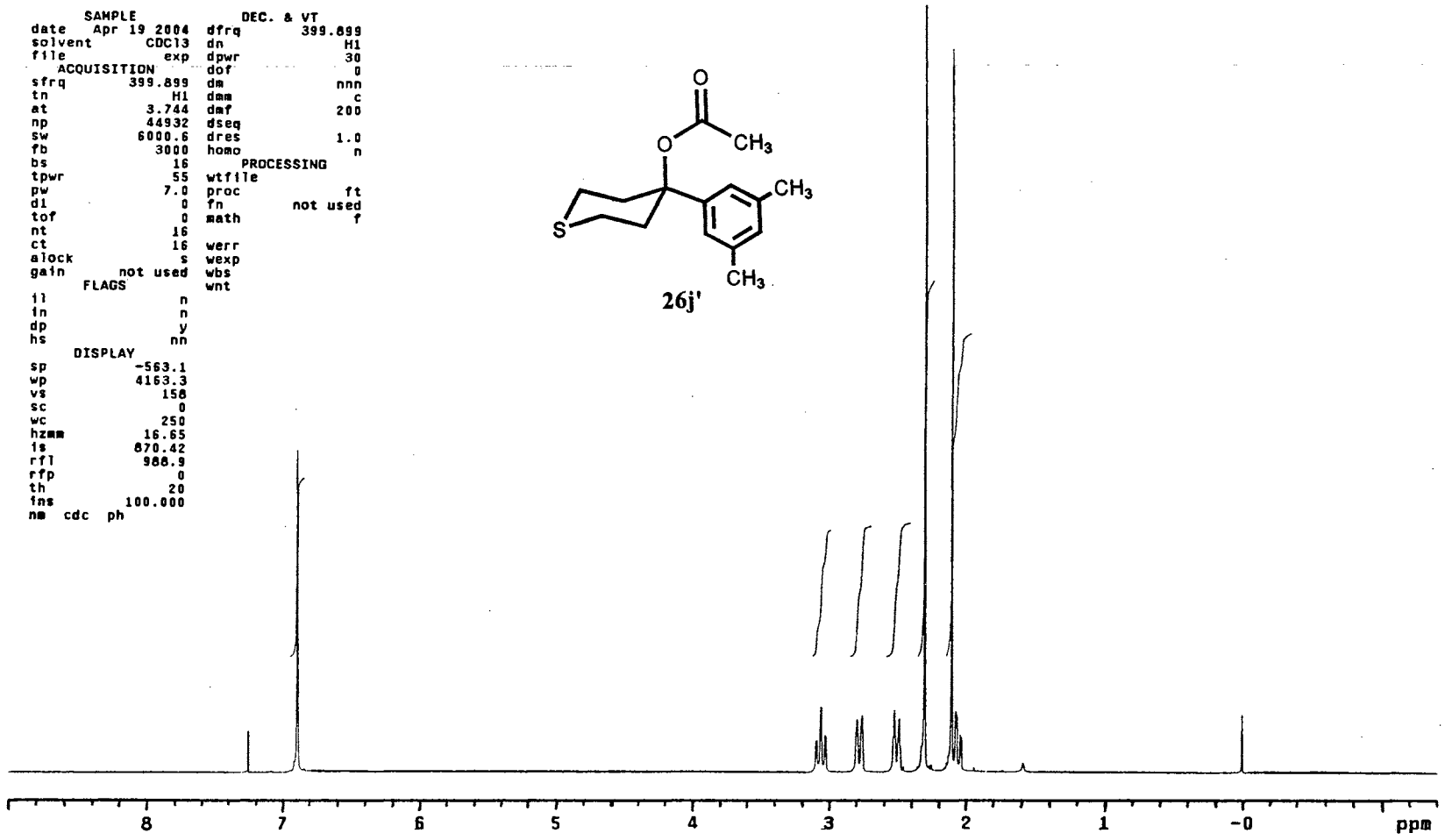
^{13}C NMR Spectrum of **28**

Plate L



IR Spectrum of **26j'**

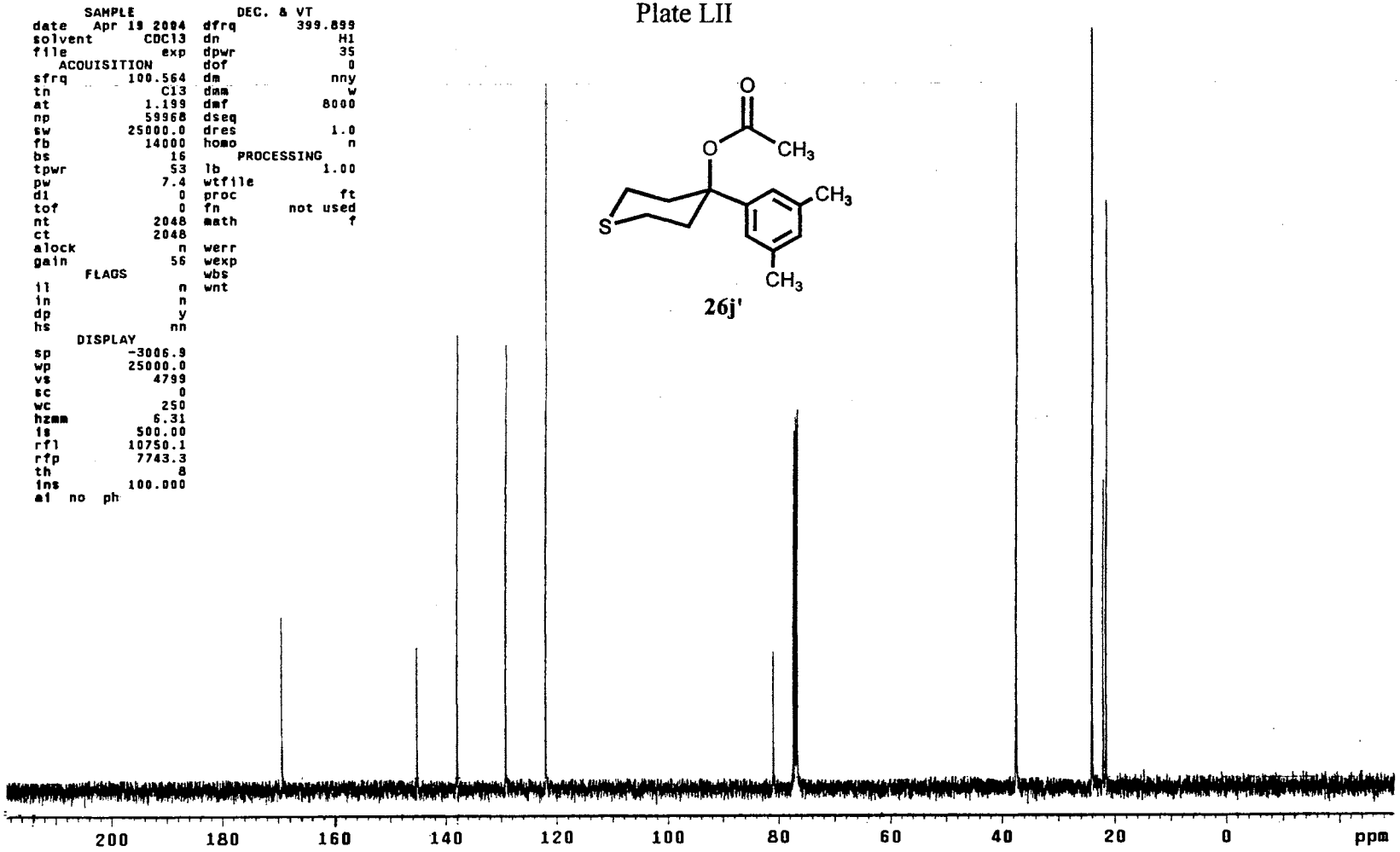
Plate LI



26j'

^{1}H NMR Spectrum of **26j'**

Plate LII



26j'

^{13}C NMR Spectrum of **26j'**

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Hydroperchlorate, and 7-Benzyl-9-phenyl-3-thia-7-azabicyclo[3.31]nonan-9-ol Hydroperchlorate and Derivatives; Single-Crystal X-ray Diffraction Analysis and Evidence for Chair-Chair and Chair-Boat Conformers in the Solid State. *J. Med. Chem.* **1984**, *27*, 758-767.

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VITA

KEVIN TRAN

Candidate for the Degree of

Doctor of Philosophy

Thesis: A Study of Synthetic Methodology, Stereochemistry, and Conformational Analysis of Selected 3,7-Diheterabicyclo[3.3.1]nonan-9-ols and Derivatives with Potential Multi-Class Antiarrhythmic Activities.

Major Field: Organic Chemistry

Biographical:

Personal Data: Born in Saigon, Vietnam, on July 18, 1974, the third son of Kent Tran and Anh Le. Married to my lovely-wife Ngoc-Khanh Nguyen, in April 2001, younger brother of Truong Tran and Kenny Tran, and older brother of Kelli Tran and Tran Tran.

Education: Graduated from Northeast High School with 1st place award in Biology, Oklahoma City, Oklahoma, in June 2, 1995; received Bachelor of Science Degree in Chemistry and Health Science from University of Central Oklahoma, Edmond City, Oklahoma, in December, 1999; completed requirements for the Doctor of Philosophy degree at Oklahoma State University in July, 2004.

Professional Experience: Teaching Assistant and Research Assistant, Department of Chemistry, Oklahoma State University, Stillwater, OK 74078

Professional Organizations: Member of the American Chemical Society, member of Division of Organic Chemistry